Myocardial Viability In Ischemic Syndromes

Cover: Two-dimensional echocardiographic enddiastolic and endsystolic still-frames of a patient before and after coronary artery bypass graft surgery, demonstrating functional recovery.

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Myocardial Viability in Ischemic Syndromes

evaluatie van diagnostische methoden naar myocardiale vitaliteit

Proefschrift

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Voor allen die mij dierbaar zijn

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Chapter 1

Introduction and Outline of the Thesis

Introduction

Background

Currently cardiologists face a substantial growth in the number of patients with congestive heart failure, a clinical syndrome with a poor prognosis. In the United States, more than 3 million people suffer from heart failure and more than 100,000 die from end-stage congestive heart failure annually.[1] In the Netherlands the prevalence of heart failure is currently 4% and rises firmly in the elderly. Although heart failure can be caused by various pathological processes, the single most frequent cause is left ventricular (LV) systolic dysfunction resulting from myocardial ischemic injury due to coronary artery disease. Myocardial dysfunction is the major determinant of the severity of heart failure and prognosis.[2-5] The risk of developing heart failure in ischemic heart disease is much lower and the prognosis better when LV systolic function is preserved. Therefore preservation of LV function by limiting infarct size or improvement of chronic ischemic LV dysfunction must be considered as major therapeutic goals for the prevention of ischemic heart failure. The introduction of aggressive reperfusion strategies in the treatment of acute myocardial infarction, such as thrombolytic therapy and direct PTCA, has dramatically improved prognosis of patients with myocardial infarctions.[6-8] Due to the progress in management of acute ischemic events, there are increasing numbers of patients with (asymptomatic) LV dysfunction. However, also in the thrombolytic era, mortality rises steeply in patients with a LV ejection fraction (LVEF) of $<35\%$.[9] Below this break point even a small gain in function may imply substantially improved prognosis.

Apart from medical therapy, available treatment options in the management of patients with coronary artery disease and advanced LV dysfunction are heart transplantation, myocardial revascularization (PTCA or CABG) and other forms of reparative surgery (i.e. mitral valve surgery, dynamic cardiomyoplasty, LV aneurysmectomy). Reparative surgery will not be discussed in this thesis.

Heart transplantation has been successfully performed in patients with end-stage heart failure. The Thoraxcenter Rotterdam has reported a five year survival rate of 84%.[10] However, in the first 9 years of the heart transplant program only 200 patients could be treated. Shortage of donor hearts and the significant morbitity of immunosuppressive therapy has led to a search for alternative treatment choices.

It is well recognized that CABG may improve LV performance and functional status in patients with chronic advanced LV dysfunction.[11] Several studies have shown that myocardial revascularization may improve regional and global LV function.[11-13] Additionally, long-term survival may improve after revascularization.[14] In patients with a LVEF $\leq 35\%$ Pigott and coworkers[14] reported a 7-year survival of 63% after CABG compared with 34% when on medical therapy. However the CABG procedure is associated with high mortality in patients with poor LV function.[15,16] Therefore careful preoperative selection of patients with poor LV function who will benefit from a revascularization procedure is warranted. Appropriate decision making prevents patients, in whom revascularization would not result in functional benefit from being exposed to high risk surgery. Distinction between dyssynergic regions containing viable and non-viable myocardium may identify patients with high and low probability to improve LV performance and functional status after revascularization, This may help the physician in clinical decision making.

Pathophysiology of myocardial dyssynergy

Several different conditions may lead to myocardial contractile dysfunction. LV dyssynergy may be due to myocardial necrosis, (repetitive) stunning or myocardial hibernation.

In myocardial necrosis scar formation involves either the entire myocardium, is limited to the subendocardium or is scattered throughout the myocardium. In all these conditions it is not expected that revascularization results in improvement of contractile function.

Myocardial stunning is defined as transient prolonged postischemic dysfunction that may occur after the restoration of normal flow.[17,18] Despite the absence of irreversible damage, mechanical dysfunction may persist after coronary reperfusion in different clinical situations following, for example coronary angioplasty,[19,20] coronary artery bypass surgery, unstable angina,[19-21] exercise-induced ischemia[22] or acute myocardial infarction with early reperfusion.[23-30] Spontaneous recovery may occur within weeks after the event and is dependent on the "area at risk", the duration of coronary occlusion, the amount and location of myocardial necrosis and the presence and extent of collateral vessels.[31] Repeated

episodes of myocardial ischemia may however also lead to a chronic reduction in contractility without a concomitant reduction in myocardial perfusion.[32,33] This phenomenon has recently been described as repetitive stunning. The impairment of contractile function can be reversed after adequate revascularization.

The concept of hibernation has been introduced by Rahimtoola. He hypothesizes that chronic reduction in myocardial blood flow may lead to a matched downregulation of the contractile cellular function which is reversible after revascularization.[34,35] It has been postulated that reduction of contractile function may be a protective response of myocytes to counteract the reduced supply of oxygen and substrates. The restoration of the delicate balance between perfusion and contraction may prevent cell death.[34-36]

In individual patients, all types of reversible and irreversible contractile dysfunction may coexist. Both experimental and clinical studies have conclusively demonstrated that the simple assessment of wall motion does not adequately distinguish non-viable from viable (either stunned or hibernating) but dyssynergic segments.[37-39]

Positron emission tomography

Among the available techniques, positron emission tomography (PET) of myocardial perfusion and metabolism (using ^{18}F-fluorodeoxyglucose (FDG)) is considered the gold standard for the identification of viable myocardium.[40-45] Under normal physiologic conditions myocardial perfusion is closely matched with the energy requirements of the myocardium. Under ischemic conditions exogeneous glucose becomes the preferred substrate for myocytes.[46,47] The rationale for the use of FDG is based on the fact that after uptake FDG is intracellularly trapped. The hallmark of jeopardized and viable myocardium is either increased FDG uptake in areas of myocardial hypoperfusion (mismatch) or, normal or increased FDG uptake in areas of normal perfusion (repetitive stunning). With these characteristics present there is a high likelihood of functional recovery after revascularization. On the other hand, a mild reduction in both perfusion and FDG uptake has also been considered to represent viable myocardium (viable match) which is however unlikely to improve in contractile performance after revascularization.[41] Comparison with myocardial biopsies have provided histological evidence for the presence

of viable tissue in dyssynergic segments with preserved FDG uptake.[32,42,48] By differentiating between perfusion-metabolism match or mismatch PET can adequately predict recovery of regional and global LV function after revascularization.[40,49-56] Furthermore, retrospective follow-up studies suggest that PET carries prognostic information.[57-61] Patients with hibernating myocardium have an increased risk to suffer cardiac events in comparison to patients without myocardium in jeopardy. The presence of a mismatch pattern in medically treated patients is associated with a higher morbidity and mortality. In these patients revascularization substantially improves symptoms related to heart failure and reduces the number of cardiac events. However high costs and limited availibility restrict the use of PET.

Alternative diagnostic methods

To respond to the increasing demand for viability studies, other techniques have been proposed including imaging myocardial FDG uptake (using special 511 keV collimators) with single photon emission computed tomography (SPECT),[62-66] 201-thallium (^{201}Tl) SPECT,[50,67-73] technetium-99m sestamibi SPECT[74] and dobutamine stress echocardiography.[74-79] These techniques are attractive from a clinical point of view, because they are widely available and may be more cost-effective. However they reflect different cellular mechanisms of viability.

During the last decade ^{201}Tl SPECT has received much attention and is now considered to be a reliable technique for the identification of viable myocardium.[80] Assessment of myocardial viability using ^{201}Tl SPECT is based on the principle that initial tracer uptake is proportional to regional flow, whereas delayed imaging reflects cell membrane integrity by demonstrating redistribution.[81] In direct comparison with PET, several different ^{201}Tl protocols (especially stress-redistribution-reinjection and rest-redistribution) have demonstrated good agreement with the detection of viable myocardium.[50,82,83] In practical terms, the most important aspect of viability is recovery of mechanical function either spontaneously or after intervention. Whether ^{201}Tl SPECT can accurately predict recovery of LV function is still unclear and will be addressed in this thesis.

Low-dose dobutamine echocardiography has been proposed as another alternative method for the assessment of residual myocardial viability both in patients

soon after acute myocardial infarction[75-77] and in patients with stable chronic ischemic heart disease.[74,78,79] The rationale is based upon the fact that low-dose dobutamine increases myocardial contractility with a minimal increase in heart rate. The inotropic effect of dobutamine is already nearly maximal at doses of 5 to 15 μg/kg/min and is dependent on infarct size, the severity of stenosis of the infarct related coronary artery and the duration of infusion. The echocardiographic hallmark for viability is improvement of contractility of a dyssynergic segment after inotropic challenge (Figure 1). The concept of metabolically viable myocardium must be distinguished from the ability to recover regional or global ventricular function. A metabolically viable myocardium does not necessarily results in functional improvement. Only that dyssynergic segment which contains a "critical mass" of stunned/hibernating myocardium, may potentially improve after coronary revascularization (Figure 2). Other potential clinical benefits of metabolic viable myocardium may be the prevention of infarct expansion or the preservation of contractile reserve. The role of dobutamine stress echocardiography, by assessing contractile reserve, in the prediction of improvement of function will be studied in this thesis.

Outline of the thesis

At present there is only one PET available for clinical use in the Netherlands. Alternative methods are evaluated to meet the clinical need to assess the viability status of the myocardium in patients with advanced ischemic LV dysfunction. Since recovery of LV function is one of the most attractive expectations of the detection of dysfunctional but viable myocardium, the aim of this thesis is to evaluate the different alternatives of PET for the identification of patients who are likely to improve in resting LV function after either myocardial infarction or myocardial revascularization.

In Chapter 2 the value of sestamibi to distinguish viable myocardium from scar tissue and to predict functional recovery will be discussed.

The concordance for the detection of myocardial viability between two currently most advocated ^{201}Tl imaging protocols has been studied. The results are described in Chapter 3.

Chapter 4 describes the safety and feasibility of high dose dobutamine-

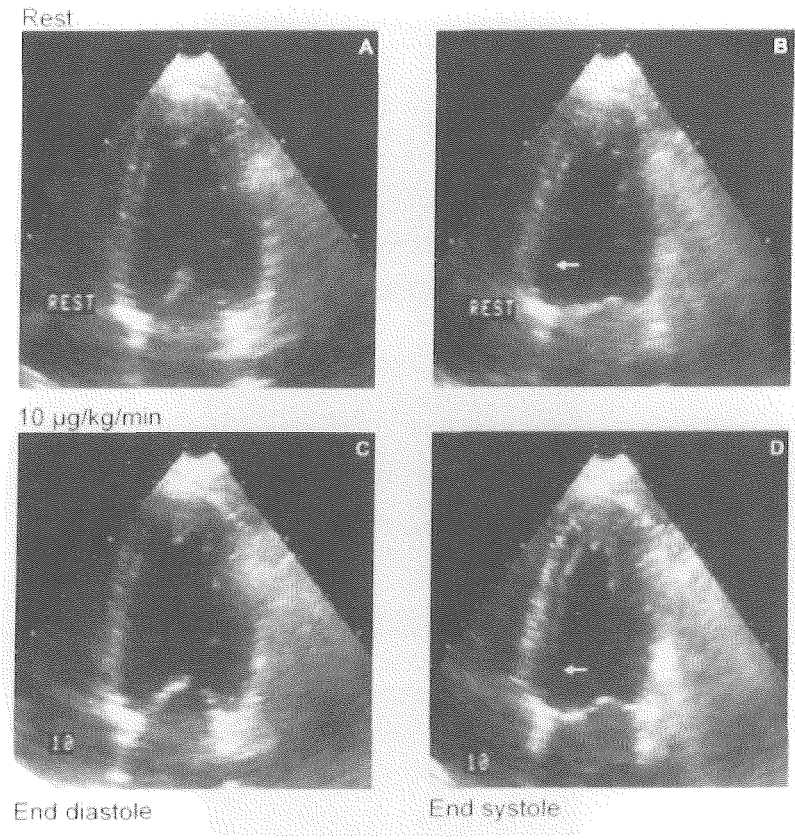

Figure 1 Representative example of myocardial viability as demonstrated by low-dose dobutamine stress echocardiography. Top panels show resting apical four-chamber views at end diastole (A) and end systole (B). Marked dyssynergy is present in the posteroseptal segment (arrow). Bottom panels show the same views during dobutamine infusion (10μg/kg/min). At end systole a clear improvement in wall thickening has occurred after the inotropic stimulus (arrow in panel D).

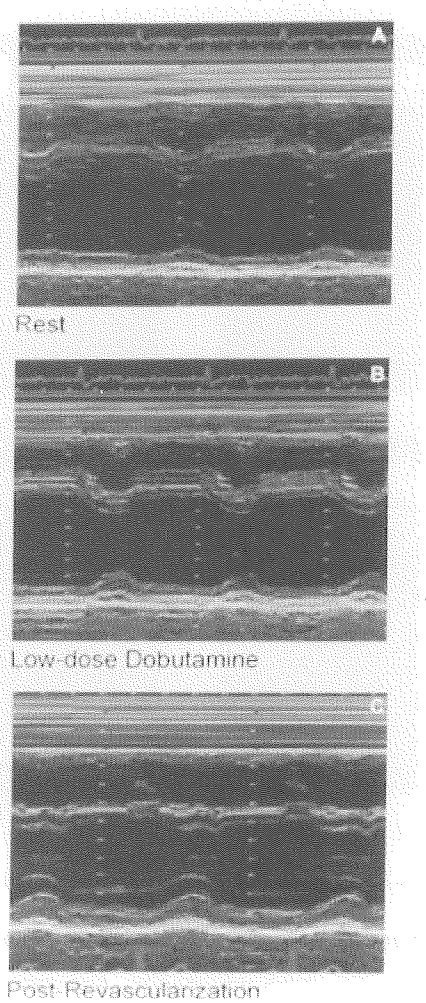

Figure 2 Example of post-revascularization improvement of posterior wall thickening as predicted by low-dose dobutamine stress echocardiography. M-mode tracings of the parasternal long axis view demonstrate at rest severe hypokinesia of the posterior wall (panel A). At low-dose dobutamine infusion wall thickening improved (panel B), after successful revascularization wall thickening at rest recovered to the level as predicted by low-dose dobutamine infusion.

atropine stress echocardiography in patients with ischemic LV dysfunction.

The second part of this thesis is dedicated to the value of the different techniques to predict recovery of LV function at rest, either spontaneously after acute MI or after revascularization in chronic coronary artery disease. The studies involved close co-operation with the Department of Cardiothoracic Surgery (Head: Prof.Dr. E.Bos) and the referring 'Rijnmond' cardiologists.

Chapters 5 and 6 deal with the value of low-dose dobutamine echocardiography and T-wave normalization for the prediction of late spontaneous recovery of regional LV function after acute myocardial infarction.

A direct comparison between low-dose dobutamine echocardiography and post-stress reinjection ^{201}Tl SPECT for the prediction of recovery of mechanical dysfunction after CABG in patients with chronic coronary artery disease is discussed in Chapter 7.

Chapters 8 and 9 describe co-operative studies with the Department of Cardiology of the Free University Hospital, Amsterdam.

The aim in Chapter 8 was twofold; 1) to evaluate the use of FDG SPECT in the prediction of functional improvement of regional and global LV function after revascularization, and 2) to compare FDG SPECT with rest-redistribution ^{201}Tl SPECT in a head-to-head fashion.

Chapter 9 describes a study designed to determine the agreement between FDG SPECT and low-dose dobutamine echocardiography to identify viable myocardium and to predict improvement of regional LV function after revascularization.

To overcome the limitations of low-dose instead of high-dose dobutamine infusion and to circumvent the methodological problems caused by the lack of an independent technique to detect changes in LV performance over time, we then designed a high-dose dobutamine/atropine echocardiographic study using radionuclide ventriculography as independent method to determine improvement of LV function (Chapter 10). In the studies described in Chapters 5 to 9 functional recovery was measured by resting echocardiography at 3 months. We realised however, that recovery in some patients may be delayed for more than 3 months, given the severity of structural changes observed in hibernating myocardium.[42] In

the study described in Chapter 10, the time course of recovery of LV function is studied in more detail by extending the follow-up period to 1 year after CABG.

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Part I

METHODOLOGY

Chapter 2

Assessment of Myocardial Viability Before Revascularization: Can Sestamibi Accurately Predict Functional Recovery?

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Introduction

The assessment of myocardial viability is an issue of considerable clinical relevance in the current era of thrombolytic therapy and coronary revascularization.[1,2] The awareness of the potential of even severe regional and global dyssynergic myocardium to improve its functional state, has resulted in a search for the optimal diagnostic approach for its noninvasive assessment. The identification of myocardial regions with high and low probability of functional improvement after revascularization is of vital importance since this can be crucial for the decision of performing revascularization procedures in individual patients with multiple severe wall motion abnormalities.

Viability, defined by reversible myocardial dysfunction, may be caused by stunning or hibernation. Myocardial stunning is transient prolonged postischemic dysfunction that may occur after the restoration of normal flow.[1] Despite the absence of irreversible damage, mechanical dysfunction may persist after coronary reperfusion in different clinical scenarios such as after percutaneous transluminal coronary angioplasty, coronary artery bypass surgery or acute myocardial infarction with early reperfusion.[3,4] Spontaneous recovery may occur within weeks and is dependent on the "area at risk", the duration of coronary occlusion and the presence and extent of collateral vessels.[5] In hibernating myocardium, chronic reduction in myocardial blood flow is thought to be matched by downregulation of the contractile cellular function.[6,7] Successful coronary revascularization may lead to functional recovery of this chronic process. In contrast, myocardial necrosis and scar tissue formation do not lead to reversibility of contractile dysfunction. In individual patients, all types of reversible and irreversible contractile dysfunction may coexist with areas of normal contractile myocardium.

Recovery of function

Although normal contractile myocardium is obviously viable, a mixture of normal myocardium with scar or hibernating myocardium can both be present in a hypokinetic myocardial region, but only that segment which hibernates may potentially improve after coronary revascularization. Thus accurate noninvasive methods are needed to discriminate between the different pathophysiologic mechanisms of hypo- or akinesis. Randomized trials in patients with coronary

Table 1 Factors influencing the recovery of left ventricular function after revascularization

. amount and degree of stunning (recent myocardial infarction, repetitive ischemia)
. amount and degree of myocardial hibernation
. presence and amount of myocardial scarring
. graftable vessels
. left ventricular plasty
. completeness of revascularization
. internal mammary arterial or vein graft
. perioperative myocardial infarction
. early graft closure
. left ventricular dimensions
. timing and method to assess regional left ventricular function
. myocarditis/cardiomyopathy

artery disease have indicated that coronary revascularization can lead to improved left ventricular function.[8] More recently it has been demonstrated, that even in severe left ventricular dysfunction, ejection fraction can improve in selected patients.[9] These results implicate the potential to prolong survival as well as the quality of life in patients with left ventricular dysfunction. Thus patients with chronic advanced ischemic left ventricular dysfunction, even when eligible for heart transplantation, may improve after successful revascularization. Several factors may affect the outcome of such approach however (Table 1). It is conceivable that in patients with hibernating myocardium, repetitive episodes of superimposed stunning exist due to transient ischemia.

Furthermore, not only the presence but more importantly the amount of myocardium in hibernation and the degree of myocardial scarring affect the outcome of revascularization.

Other factors mentioned in Table 1 but important to keep in mind are the success of revascularization and the preoperative left ventricular dimensions. Patients with severe left ventricular dilatation may be less likely to recover. Anyway, recovery of ventricular function may underestimate the real extent of myocardial viability due to sometimes inadequate restoration of regional

myocardial blood flow. Various nuclear methods have received attention for the assessment of myocardial viability. This chapter focusses on the approach with technetium-99m (Tc-99m) labeled sestamibi as a perfusion agent to (1) distinguish hibernation (with or without superimposed stunning) from non-viable myocardium and (2) to predict functional recovery after coronary revascularization.

Properties of Tc-99m sestamibi

Sestamibi is a Tc-99m labeled myocardial perfusion agent, providing similar information as thallium-201 (^{201}Tl) for the detection of coronary artery disease.[10] In comparison with ^{201}Tl, sestamibi has the advantage of better imaging properties, particularly when single photon emission computed tomography (SPECT) is considered.[11] The gamma emission of Tc-99m sestamibi is higher (141 keV versus 68 to 80 keV) and its physical half life is shorter (6 versus 73 hours). Another difference between ^{201}Tl and sestamibi is the lower first pass extraction for sestamibi (40% versus 80%).[11,12] Although minimal myocardial redistribution occurs (<25% in 4 hours), the slow myocardial clearance of sestamibi compensates for its low first pass extraction.[13] The tissue uptake of sestamibi is parallel to coronary blood flow, with the exception of high flow conditions. Even under conditions of low coronary blood flow and in stunned myocardium, the myocardial uptake of sestamibi is comparable with that of ^{201}Tl.[14] Since the uptake of sestamibi is dependent on cell membrane integrity and mitochondrial function (membrane potential), it may from a cellular point of view also reflect myocardial viability.[15]

While the use of sestamibi for myocardial perfusion is well accepted, its role for the assessment of myocardial viability is still controversial.[2,11,16] On the basis of these experiments, one may expect that sestamibi is comparable to ^{201}Tl for the detection of viable, stunned myocardium, when myocardial perfusion has been restored after an ischemic episode. In contrast, ^{201}Tl seems more suitable than sestamibi in the setting of hibernating myocardium, due to its properties to redistribute in a chronic low flow state.[16] In this condition, a sestamibi scan at rest is expected to show a perfusion defect, most likely underestimating the presence of viable myocardium. However, in the clinical setting stunned and hibernating myocardium often coexist and constitute a dynamic condition. Therefore, a

distinction between the 2 syndromes is more theoretical than real in our daily clinical practice.

Sestamibi in chronic left ventricular dysfunction

Several recent publications describe the merit of sestamibi in the setting of chronic ischemic left ventricular dysfunction in order to distinguish viable myocardium from scar. There are two kinds of data available: first, comparative studies between sestamibi and other viability tracers like ^{201}Tl[17-24] or ^{18}F-FDG using positron emission tomography[25,26] and second, studies using the improvement of left ventricular wall motion after succesful revascularization as a standard for myocardial viability.[27-33]

Comparison of sestamibi with ^{201}Tl

All studies comparing sestamibi and ^{201}Tl have reached similar conclusions, suggesting that myocardial regions with severely reduced sestamibi uptake at rest may contain viable tissue. Post-stress reinjection ^{201}Tl imaging has been compared with sestamibi imaging at rest by different authors.[17-19] Cuocolo et al[17] compared exercise-redistribution-reinjection with exercise-rest sestamibi (two day protocol) planar imaging in 20 patients with coronary artery disease and chronic left ventricular dysfunction (ejection fraction 30 $\pm$ 8%). Qualitative segmental analysis showed 122 myocardial segments (41%) with irreversible ^{201}Tl uptake defects at redistribution. After ^{201}Tl reinjection, in 57/122 of these segments (47%) tracer fill-in was noted. In contrast, 100/122 segments appeared as fixed defects (without reversibility) on the sestamibi images at rest. Furthermore, the resting sestamibi mean uptake score in the segments with perfusion defects was significantly worse compared to the reinjection ^{201}Tl mean uptake score (5 point grading system).

Since quantitative analysis of SPECT images may improve diagnostic accuracy of comparative data, 26 patients with advanced chronic left ventricular dysfunction (mean ejection fraction 32 $\pm$ 6%) due to coronary artery disease, were studied with post-stress reinjection ^{201}Tl as well as sestamibi SPECT at rest within 7 days.[19] The images were acquired 20 minutes after reinjection of 40 MBq of ^{201}Tl and 2 hours after intravenous administration of 370 MBq of sestamibi. All images were acquired using a single head rota gamma camera with a low-energy, all

Table 2 Quantitative analysis of perfusion defect severity (unitless, mean ± standard deviation) using SPECT in 26 patients with chronic left ventricular dysfunction due to coronary artery disease: a comparison between sestamibi and ^{201}Thallium

Sestamibi at rest	3627 ± 1587
^{201}Thallium reinjection	2553 ± 1309 *

* $p < 0.005$ versus sestamibi

purpose collimator. Thirty-two projections (180° scanning) were obtained with an acquisition time of 45 s/projection. Quantitative analysis was performed by circumferential profile analysis of six standardized short axis slices. The profiles were defined within the automatically detected endo- and epicardial boundaries. The normal limits for sestamibi and ^{201}Tl were separately defined within 2 standard deviations of profiles (regional values) from a normal database. Perfusion defects were calculated by summing the areas below the lower limit of normal in the six short axis slices. The results, summarized in Table 2 and Figure 1, indicate that sestamibi uptake defects were systematically more severe compared to the reinjection ^{201}Tl uptake defects (sestamibi = 1337 + 0.9 thallium; r = 0.74). This finding reinforces the idea that sestamibi may underestimate the extent of residual myocardial viability.

Several small studies recently compared sestamibi imaging at rest with rest-redistribution ^{201}Tl imaging.[20-24] Cuocolo et al[20] reported in 19 patients 48 segments with severe sestamibi perfusion defects. In 26/48 segments redistribution (4 hours) ^{201}Tl revealed signs of viable tissue. These results are in agreement with other reports.[21-24] Taylor et al[22] found in 32 patients 167 severe fixed defects (SPECT) with sestamibi, but 87 (52%) demonstrated ^{201}Tl uptake on 24-hour redistribution imaging and thus suggested viable myocardium undetected by sestamibi. To circumvent the limitations of sestamibi, Maurea and coworkers [23,24] reported the use of nitrates and delayed sestamibi imaging (redistribution). However, despite redistribution (5 hours) in 25% of the moderate to severe sestamibi uptake defects and similar results after nitrates, sestamibi still underestimates myocardial viability

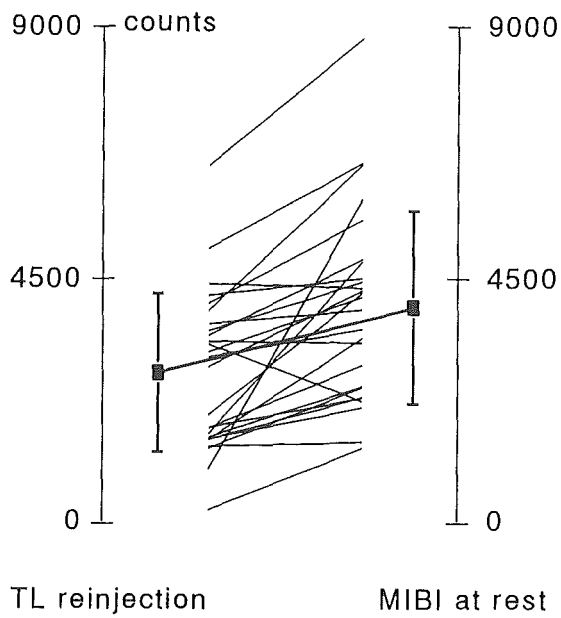

Figure 1 Graph which displays the comparison of quantitative analysis between the severity of uptake defects from resting sestamibi and post-stress reinjection ^{201}Tl SPECT in 26 patients with chronic left ventricular dysfunction due to coronary artery disease. The data show a systematic overestimation of the defect severity by sestamibi across the whole range of defect sizes.

compared to rest-redistribution ^{201}Tl in chronic coronary artery disease.

Recently, Dilsizian et al[18] have compared the value of exercise/redistribution reinjection ^{201}Tl tomography with same day rest/exercise sestamibi tomography for the assessment of myocardial viability in 54 patients with a mean ejection fraction of 34 $\pm$ 14%. They found that 36% of the reversible ^{201}Tl defects were determined to be irreversible on the stress/rest sestamibi studies. However, the same authors found that the concordance between ^{201}Tl and sestamibi increased from 75% to 93% if not only the reversibility of the perfusion defects but also a mild-to-moderate reduction in sestamibi (51 to 85% of normal activity) was considered suggestive of myocardial viability. Also, the discordance between ^{201}Tl and

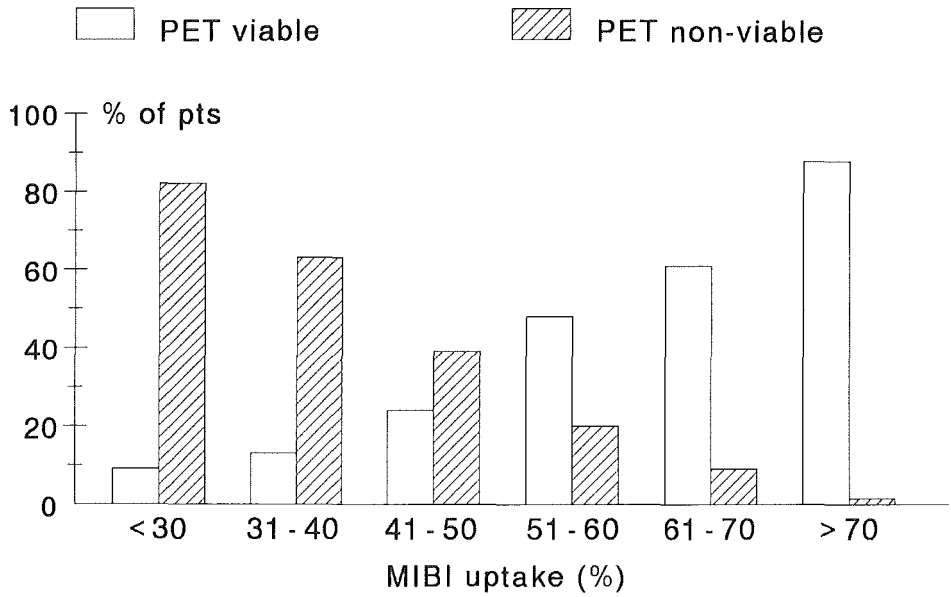

Figure 2 Results of the comparison between sestamibi uptake at rest and FDG PET derived from 111 patients with chronic coronary artery disease and wall motion abnormalities, from Altehoefer et al.[25] It displays the percentage of viable (FDG uptake >70% and nonviable (FDG uptake <50%) segments in relation to sestamibi defect severity. The sestamibi uptake, even when severely reduced (<50%), clearly underestimates the extent of viable myocardium when FDG PET is considered the "golden standard".

sestamibi diminished if an additional 4-hour redistribution image was acquired after the injection of sestamibi at rest.

Thus, the concordant results of the comparative studies using different imaging protocols suggest that sestamibi may underestimate the presence of severely hypoperfused but still viable myocardium in patients with chronic coronary artery disease. However, new data suggest that when quantitative analysis is used and late imaging is added after the resting injection of sestamibi, the differences in results obtained with ^{201}Tl and sestamibi are smaller.

Comparison with F-18 FDG PET

Recently, Altehoefer et al[25] evaluated the relationship between sestamibi uptake at rest and glucose metabolism by FDG PET. They found, in a group of 111 patients with coronary artery disease and wall motion abnormalities, preserved glucose metabolism (FDG uptake >70%) in a substantial number of patients with reduced sestamibi uptake at rest (SPECT). Furthermore, of the myocardial segments with 31-70% of peak sestamibi uptake (moderate to severe defects) 13-61% were viable by PET criteria (Figure 2). On the other hand, sestamibi defects with ≤ 30% of peak activity are highly predictive for scar tissue (82%).

Thus, the severity of a given sestamibi perfusion defect may yield an indirect estimate of the likelihood of myocardial viability. Nevertheless, 30% of the patients had at least 1 viable segment with severely reduced uptake of sestamibi (<50% of peak activity). Similarly, Sawada and coworkers[26] showed in 20 patients (7 after recent myocardial infarction) that 50% of the moderate or severe sestamibi defects had preserved glucose metabolism (>60% FDG uptake). They found no lower limit of sestamibi activity that excluded significant FDG uptake. Thus, sestamibi uptake clearly underestimates myocardial viability in comparison with FDG PET in patients with chronic coronary artery disease. These data are in agreement with the comparative data with various ^{201}Tl imaging protocols as previously discussed. However, regardless of the lower sensitivity of sestamibi for detecting viable myocardium, tracer uptake may still allow for correct prediction of functional recovery after successful revascularization. The extent of underestimation is of key importance since failure to detect limited amounts of viable myocardium may not have an impact on the outcome of revascularization.

Dilsizian et al[18] have recently found in 25 patients that the agreement between same day rest/exercise sestamibi and PET imaging (FDG/blood flow matching) is greatly enhanced if an additional late redistribution imaging is acquired after the resting injection of sestamibi or if the severity of the sestamibi activity within the irreversible defects is taken into account. However, larger comparative studies are needed to answer the question to what myocardial extent sestamibi underestimates myocardial viability relative to the amount of myocardial scar.

Can sestamibi reliably predict functional recovery after revascularization?

The number of studies dealing with this topic is limited.[27-33] The results indicate, although small numbers of patients were studied, that sestamibi is not always a good indicator of functional recovery after revascularization. In particular, Maublant et al[28] observed, in a group of 18 patients, that wall motion improved in 8 of 9 segments with a initial severe sestamibi defect 3 months after revascularization. Marzullo and coworkers[29] studied 14 patients with chronic coronary artery disease before and 3 months after revascularization. Sestamibi uptake at rest and planar rest-redistribution (16 hour) ^{201}Tl-scans were acquired before revascularization. Compared to delayed redistribution ^{201}Tl imaging, sestamibi uptake had a lower sensitivity (75 vs 86%) and specificity (84 vs 92%) to predict recovery of wall motion. Sciagrà et al[31] reported their initial results with the use of an infusion of nitrates during tracer injection. They studied in 22 patients the recovery of function after revascularization with first-pass radionuclide ventriculography. They showed a predictive accuracy for sestamibi SPECT of 82%. This approach is of interest and confirms previous work by Galli and coworkers[32] and Maurea et al[23] also using sestamibi and Medrano et al[34] utilizing ^{201}Tl reinjection. Zafrir and collegues[35] demonstrated in 18 patients with severe left ventricular dysfunction the additional value of simultaneous assessment of function and perfusion by sestamibi for the prediction of functional recovery. A recent study from Udelson et al[33] performed a head-to-head comparison between rest-redistribution ^{201}Tl tomography and rest injection of sestamibi (with imaging 1 hour post-injection), to predict the recovery of regional left ventricular dysfunction after successful revascularization. Thirty-one patients were studied with echocardiography before and on average 20 days after revascularization. ^{201}Thallium and sestamibi had similar positive (75% for ^{201}Tl and 80% for sestamibi) and negative (92% and 96%, respectively) predictive values for recovery of regional left ventricular dysfunction after revascularization. For both tracers, the "best" cut-off for the discrimination of viable and not viable myocardium was 60% of peak activity. These excellent results are somewhat surprising because sestamibi scintigraphy was acquired with no pre-medication of nitrates nor was late imaging performed.[18] These results, although very promising, should be viewed with some caution because of 1) the very short follow-up of 20 days after revascularization,

and 2) the lack of information on the changes of global left ventricular function after revascularization.

Conclusion

Myocardial perfusion imaging may reflect viability, since tracer uptake requires adequate perfusion, cellular integrity and metabolic function. 99m-Technetium is an excellent myocardial flow tracer, but from the data so far available it seems less suitable than ^{201}Tl for the assessment of myocardial viability in chronic coronary artery disease. It tends to overestimate the extent of myocardial necrosis or scar.

However, since sestamibi possesses superior imaging properties, the underestimation of myocardial viability has lead to the development of alternative protocols. For the detection of viable myocardium, imaging 1 hour after sestamibi injection may not be optimal. The tracer is known to redistribute to a small degree, thus delayed imaging may enhance the detection of viable myocardium in severe perfusion defects.[13,18] Furthermore, nitroglycerin administration before rest imaging seems useful[23,32] and also with the addition of functional data (first pass and/or gated imaging), revealing a complementary data set on function and perfusion, the proper identification of viability may be improved.[27,35] Quantification of regional tracer uptake may also enhance the discrimination between viable and non-viable myocardium.[18,25,27,33] However, even with quantitation, a significant amount of severe defects still represents viable tissue.[25,29] Finally, new methods for attenuation correction may reduce the number of artifacts, in particular false positive perfusion defects, in order to enhance diagnostic specificity.

Thus, although it seems that sestamibi SPECT with 1) quantification of the activity, 2) late imaging and 3) pre-medication with nitrates provides information on myocardial viability close to that of ^{201}Tl and PET, further studies are needed to substantiate the usefullness of sestamibi for addressing the issue of viability. In particular we feel that the role of sestamibi for the prediction of functional recovery after revascularization has still to be defined in larger and possibly multicenter studies.

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Chapter 3

Dobutamine Stress-Redistribution-Reinjection Versus Rest-Redistribution ^{201}Thallium SPECT in the Assessment of Myocardial Viability

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Abstract

The aim of this study was to evaluate the value of thallium-201 chloride (^{201}Tl) reinjection imaging following dobutamine stress (DRi) to identify viable myocardium in comparison with a rest-redistribution ^{201}Tl protocol (RR).
The identification of viable myocardium bears important consequences for adequate selection of patients with poor left ventricular function, often unable to exercise, who are considered for revascularization.

Twenty-six patients with chronic coronary artery disease and depressed left ventricular function (ejection fraction 36 $\pm$ 10%) were studied by both DRi and RR single photon emission computed tomography (SPECT). Semi-quantitative analysis of regional ^{201}Tl activity (5-point score) and wall motion by echocardiography using a 16-segment model was performed. Regions were classified as viable (normal/reversible/fixed moderate defects) or nonviable (fixed severe defects) and related to regional wall motion. Target heart rate was reached in 25 patients. Myocardial viability was demonstrated in 353/416 (85%) by DRi SPECT and in 346/416 (83%) by RR SPECT. The agreement between the 2 protocols was 98% with a K value of 0.94; similar results were obtained when the analysis was limited to dyscontractile segments.

In conclusion, this study confirms the feasibility and diagnostic value of DRi SPECT to identify viable myocardium.

Introduction

In patients with coronary artery disease, dyscontractile myocardium may represent either viable or necrotic myocardium.[1] Recovery of regional contractile function after revascularization may occur when residual viability is present, whereas necrotic myocardium will not improve in function.[1] If a substantial amount of dyscontractile but viable myocardium is present, this may translate in improvement of global ventricular function.[2-4] Thus, the identification of viable myocardium bears important consequences for adequate selection of patients considered for revascularization. This is even more important in patients with severely depressed ventricular function, since surgical intervention in this subset of patients is associated with high mortality[5], and also improves long-term survival as compared to conservative treatment.[6]

At present, many laboratories use the potassium analogue thallium-201 chloride (^{201}Tl) to assess cellular integrity, hence indicating viability. Both ^{201}Tl rest-redistribution[4,7-10] and stress-redistribution-reinjection[11-13] are frequently used protocols to assess myocardial viability. Stress-redistribution-reinjection provides information on both stress-induced ischemia and viability, whereas rest-redistribution provides only information on viability.

Previous studies employed physical exercise to provoke myocardial ischemia using the stress-redistribution-reinjection protocol.[11-13] Since patients with advanced left ventricular dysfunction are often unable to exercise, pharmacological stress with adenosine,[14] dipyridamole[15] or dobutamine[16] has been be used as an alternative to induce myocardial ischemia. The value of a ^{201}Tl reinjection protocol using pharmacological stress to assess myocardial viability is unclear, although a major difference with maximal exercise testing is unlikely. No comparative studies between such protocol and positron emission tomography or ^{201}Tl rest-redistribution single photon emission computed tomography (SPECT) have been described.

Therefore, the aim of the present study was to evaluate the value of ^{201}Tl reinjection imaging following dobutamine infusion to identify viable myocardium using rest-redistribution ^{201}Tl imaging as a reference method.

Methods

Study population

We studied 26 patients with chronic coronary artery disease and depressed LV function (mean left ventricular ejection fraction 36 $\pm$ 10%). All patients underwent two-dimensional echocardiography, cardiac catheterization, dobutamine stress-redistribution-reinjection and rest-redistribution SPECT.

The patients had a mean age 60 $\pm$ 7 years; there were 20 men and 6 women. Twenty-three of the study patients (88%) suffered a previous myocardial infarction, but not within 6 months before the study (mean 62 $\pm$ 64 months, range 6-228). Twenty-one patients had a Q wave on the ECG (10 anterior, 11 inferior). All patients were symptomatic. Fifteen patients were in New York Heart Association functional class II and 11 in class III.

In each patient coronary angiography showed significant narrowing ($\geq$50% reduction in luminal diameter) of at least one major coronary artery. Three patients

had single vessel disease, 5 had two-vessel disease and 18 had 3-vessel disease. Informed consent was obtained in all patients. The study protocol was approved by the ethical committee of the University Hospital Rotterdam.

Two-dimensional echocardiography

Echocardiography was performed with a commercially available scanner (Vingmed CFM 800). Standard views of the left ventricle (parasternal long- and short-axis, apical 2- and 4-chamber views) were recorded. To evaluate regional wall motion, the left ventricle was divided into 16 segments, as previously described.[17] The interpretation was done by two experienced observers who were blinded to the nuclear data of the individual patients. Each segment was scored semiquantitatively as: 1 = normal (normal endocardial excursion and systolic wall thickening), 2 = hypokinesia (moderate to severe reduction in excursion and wall thickening), 3 = akinesia (absence of excursion and wall thickening) or 4 = dyskinesia (paradoxic outward movement in systole). We previously reported the good inter- (84%) and intraobserver (87%) concordances of resting wall motion analysis of our laboratory.[18]

Dobutamine stress-redistribution-reinjection ^{201}Tl SPECT

Increasing doses of dobutamine were infused through an antecubital vein with steps of 10 ug/kg/min every 3 min to a maximum of 40 ug/kg/min. Atropine (up to 1 mg) was given if there were no signs of ischemia and if the 85% of the age predicted maximal heart rate was not reached. The test was interrupted prematurely if severe chest pain, >2mm ST-segment deviation, significant tachyarrhythmias, severe hypotension or other severe unsuspected side effects occurred. Approximately 1 min before termination of the test an intravenous dose of 2 mCi of ^{201}Tl was administered.

The acquisition of the stress ^{201}Tl SPECT imaging was started within 10 min after completing the dobutamine-atropine stress test. SPECT imaging was performed on a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp.,Iselin,N.J.). For each study, 32 projections were obtained in a 180° orbit beginning from the 40° left posterior oblique to the right anterior oblique projection with an acquisition time of 60 seconds per projection. The images were

obtained using a low energy, all purpose collimator. A energy window of 20% was centered on the 68-80 keV peak. Images were stored on a 64x64, 16-bit matrix. A Gamma 11 computer system was used to process the tomographic data. Long- and short-axis tomograms were constructed from the 3-dimensional voxel matrix. Four hours after stress imaging, a redistribution image was obtained, followed by reinjection of 1 mCi of ^{201}Tl. A third acquisition was started 20 min after reinjection. In 8 patients the acquisition of a redistribution image was omitted.

Rest-redistribution ^{201}Tl SPECT

A rest-redistribution study was performed within 10 days of the stress-reinjection protocol. A single dosis of 3 mCi ^{201}Tl was administered at rest. SPECT data were acquired within 10 min after tracer injection and 4 hours later. The same camera system and acquisition protocol as described above were used.

SPECT data analysis

As previously described,[18,19] the interpretation of the images was based on six short-axis slices, three longitudinal long-axis slices and three transverse long-axis slices (for each study). The analysis was performed visually with the assistance of quantitative measurement (circumferential profiles). The same 16-segment model used for the interpretation of the echocardiograms was applied for the interpretation of the SPECT images.[18,19] ^{201}Tl uptake in each segment was scored with the consensus of 2 experienced observers using a 5-point scoring system: 0 = normal uptake, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = absent uptake.

In the stress-protocol, a segment with reduced ^{201}Tl uptake at stress was considered reversibly ischemic (viable) if the defect showed fill-in on the redistribution or reinjection image. A defect was considered fixed in the absence of fill-in. These fixed defects were divided into mild-moderate and severe defects. A defect was classified as severe if the ^{201}Tl uptake of a segment was $\leq$50% compared to maximal activity on the quantitative circumferential profile analysis[20] and if it was consistent with a severe visually assessed defect. Severe fixed defects were considered nonviable, whereas mild-moderate fixed defects were considered viable.[20] Similar criteria for the identification of viable myocardium were used in

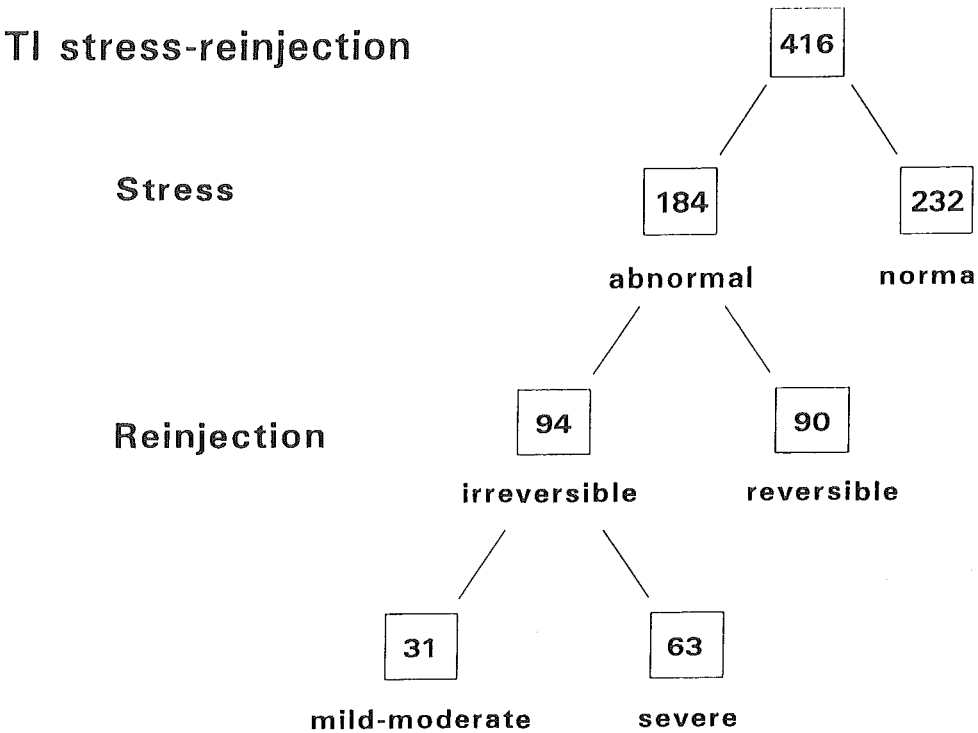

Figure 1 Diagram demonstrating the occurrence of abnormal and normal regional ^{201}Thallium activity on dobutamine stress imaging and subsequent irreversibility or reversibility after reinjection. The irreversible ^{201}Thallium defects are divided according to defect severity into mild to moderate and severe.

the rest-redistribution protocol.

Statistical analysis

Continuous data are expressed as mean $\pm$ SD. Student's *t*-test was used for comparison of paired data. Weighted K values were calculated to measure agreement between the rates of viability between the stress- and the rest-redistribution protocol. A p-value <0.05 was considered significant.

Results

Dobutamine stress test

Beta-blockade was continued in 10 of 26 patients. Seventeen patients experienced angina during the test. Target heart rate was reached in 25 patients (dobutamine infusion was discontinued prematurely in 1 patient due to symptomatic hypotension). Atropine was administered in 11 patients in order to reach the target heart rate. The mean heart rate increased from 73 ± 13 to 139 ± 15 beats/min ($p < 0.001$). Systolic blood pressure did not change significantly (130 ± 21 to 125 ± 20 mm Hg). The rate pressure product increased from 9638 ± 2953 to 17268 ± 3022 ($p < 0.001$).

Stress-redistribution-reinjection ^{201}Tl SPECT

The initial 18 patients underwent the complete protocol, whereas in the last 8 patients the redistribution image was omitted.

In 18 patients, 288 segments were evaluated, of which 154 (53%) showed no perfusion abnormalities, 42 (15%) were reversible and 92 (32%) showed irreversible defects at the conventional redistribution images. At reinjection, 29 (32%) of the 92 fixed defects demonstrated significant fill-in. Of the 63 fixed defects at reinjection, 22 were classified as mild-moderate (>50% ^{201}Tl uptake) and 41 as severe (≤50% ^{201}Tl uptake). Thus, 247 (86%) of the segments were classified as viable and 41 (14%) as nonviable. Omission of the conventional redistribution image did not change the identification of viable segments.

In the entire group of 26 patients, viability was then assessed using the stress and reinjection images only (Figure 1). In a total of 416 analyzed regions, 184 had a perfusion defect at stress, with 90 (49%) being reversible and 94 (51%) irreversible. Of the irreversible defects at reinjection, 31 (33%) were mild-moderate and 63 (67%) were severe. Hence, in the entire patient group (n = 26) 15% (63/416) of the segments were identified as nonviable.

Rest-redistribution ^{201}Tl SPECT

With the rest-redistribution protocol, 252 (61%) of the 416 segments had normal ^{201}Tl uptake and 164 (39%) showed a perfusion defect at rest (Figure 2). Of these perfusion defects 28 (17%) demonstrated reversibility at redistribution and

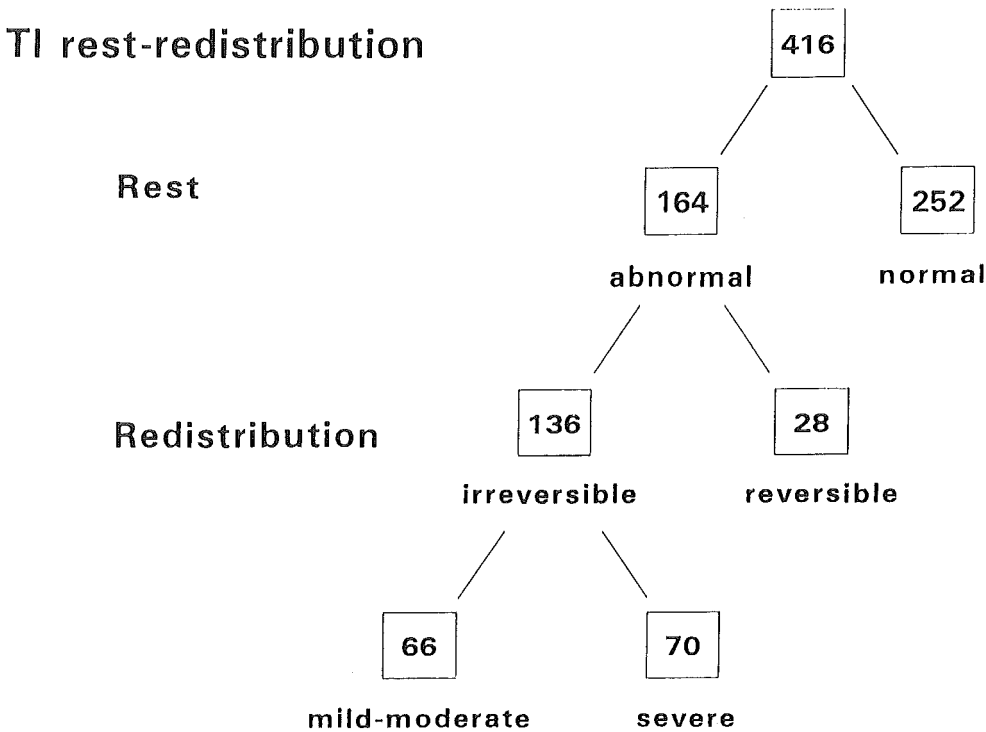

Figure 2 Diagram demonstrating the occurrence of abnormal and normal regional ^{201}Thallium activity early after tracer administration at rest and subsequent irreversibility or reversibility after four hours of redistribution. The irreversible ^{201}Thallium defects are divided according to defect severity into mild to moderate and severe.

136 (83%) remained irreversible. Seventy (51%) of the 136 fixed defects had severely reduced uptake with $\leq$50% ^{201}Tl activity. Therefore, rest-redistribution imaging identified 17% (70/416) of the segments as nonviable.

Comparison between the two protocols

Both protocols revealed similar diagnostic information in 409 of the 416 segments (Figure 3A). The agreement between the 2 protocols was 98% with a

Tl stress-reinjection

Tl rest-red	viable	nonviable		viable	nonviable
	346	0	viable	160	0
	7	63	nonviable	7	60

A

All segments
(n = 416)
Agreement 98%
K value 0.94

B

Dyssynergic segments
(n = 227)
Agreement 97%
K value 0.92

Figure 3 Concordance and disconcordance between dobutamine stress-redistribution-reinjection ^{201}Thallium SPECT and rest-redistribution ^{201}Thallium SPECT in all regions (*A*) and in dyssynergic regions (*B*) for the identification of myocardial viability.

K value of 0.94. In 7 segments stress-reinjection imaging showed viability whereas rest-redistribution imaging showed non-viability.

Since viability is mainly important in dyscontractile myocardium, we related myocardial viability to regional wall motion. On echo, 119 (29%) segments were identified as hypokinetic, 105 (25%) as akinetic and 3 (1%) as dyskinetic. A mean of 8.6 ± 4.8 dyscontractile segments per patient were identified. In the 227 segments with wall motion abnormalities, the agreement between both imaging protocols was 97% (NS versus all segments) with a *K* value of 0.92 (Figure 3B).

Relation between myocardial viability and severity of coronary artery stenosis

To assess the relation between the severity of a coronary artery stenosis and the presence/absence of myocardial viability with both protocols, the dyscontractile segments were divided into 2 groups. The analysis was limited to the 220/227 segments showing concordant information on both protocols. Group I included 31 segments supplied by a $<50\%$ stenosis; 105 segments were supplied by a 50-99%

Table 1 Relation between coronary anatomy and myocardial viability in dyscontractile segments

	Group I (n = 31)	Group II (n = 105)	Group III (n = 84)
viable	31	82	47
nonviable	0	23	37

Group I: segments supplied by < 50% coronary artery stenosis, Group II: segments supplied by a 50 - 99% coronary artery stenosis, Group III: segments supplied by a totally occluded artery.

stenosis (group II) and 84 segments were supplied by a totally occluded coronary artery (group III) (Table 1). Interestingly, myocardial viability was observed in 47/84 segments supplied by a totally occluded coronary artery.

Discussion

Myocardial viability is clinically primarily important in patients with multiple severely hypokinetic or akinetic regions leading to advanced global dysfunction and often to the inability to perform a maximal exercise test. Alternatively, in this subset of patients dobutamine stress can be employed to assess inducible myocardial ischemia and viability.[16,21,22] The present study confirms the feasibility of the dobutamine stress test even in the setting of extensive coronary artery disease and demonstrates its use to identify both ischemic and viable myocardium applying stress-redistribution-reinjection ^{201}Tl SPECT. An excellent agreement concerning the viability status of the myocardium between this protocol and a standard rest-redistribution ^{201}Tl SPECT approach was found, even after omission of the post-stress redistribution scan. Furthermore, the high level of agreement sustained when the analysis was limited to dyscontractile myocardial regions.

The favourable safety and feasibility profile of the high dose dobutamine stress test in patients with coronary artery disease even in the presence of a poor left ventricular function has encouraged its use to assess myocardial ischemia

and/or viability using echocardiography or SPECT as imaging modality.[16-18,21-23] Dobutamine is a selective β_1-adrenoceptor agonist with relatively weak α and β_2-adrenoceptor activity. Its inotropic and chronotropic effects at high-dose infusion act as an exercise simulator.[24] In comparative studies dobutamine induces reversible perfusion defects very similarily in direct comparison to maximal exercise.[22,25,26] Therefore this test is increasingly used to assess myocardial ischemia.[16,19,21]

Two studies have already demonstrated an excellent agreement between exercise-redistribution-reinjection imaging and rest-redistribution imaging for the assessment of myocardial viability[27,28] in patients with advanced coronary artery disease. The results of the present study are in line with these reports. It shows that also semi-quantitative dobutamine-redistribution-reinjection ^{201}Tl SPECT provides concordant information regarding myocardial viability when compared with a conventional rest-redistribution ^{201}Tl protocol. The use of semi-quantitative analysis of the SPECT data is crucial to reach such high concordance.[20,27,28]
However the induction of myocardial ischemia/dysfunction may limit the proper assessment of the amount of potential reversible dyscontractile myocardium. Therefore, the in the literature reported diagnostic accuracy of rest-redistribution ^{201}Tl SPECT for predicting recovery of LV function after revascularization is somewhat higher and less variable in comparison with stress-reinjection ^{201}Tl SPECT.[29]

Our results demonstrate that omission of the post stress redistribution image did not substantially change the level of concordance. Dilsizian and Bonow[30] decribed the phenomenon of "differential uptake", indicating the magnitude of change in ^{201}Tl activity after reinjection in segments identified as abnormal at stress. The authors showed that apparent washout occurred after reinjection in a small number of segments (8%) identified as abnormal at stress. Due to differential uptake, regions with fill-in at redistribution may appear fixed at reinjection when deleting the conventional redistribution image. Such segments however had a mean ^{201}Tl activity of 58% at reinjection.[30] In another study, Dilsizian et al[20] indicated that segments with ^{201}Tl activity $>50\%$, although fixed, were viable as compared with PET imaging. In our study fixed defects with a ^{201}Tl activity $>50\%$ were defined as viable, thereby circumventing the problem of underestimation of viability due to differential uptake. Viable myocardium was demonstrated in 56%

of the dyscontractile segments supplied by a totally occluded coronary artery. This finding is not surprising since the metabolic state of the myocardium is not fully dependent on the status of the epicardial coronary arteries. The presence of collateral blood flow may also play an important role in the maintenance of cellular integrity.[31] In our study we did not have the opportunity to compare the results of both ^{201}Tl protocols with positron emision tomography, nor with functional recovery after successful revascularization.

In conclusion, an excellent agreement between semi-quantitative dobutamine-redistribution-reinjection ^{201}Tl SPECT and conventional rest-redistribution ^{201}Tl SPECT to distinguish viable from necrotic myocardium was found. The high level of agreement sustained when the analysis was limited to dyscontractile myocardial regions.

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Chapter 4

Safety and Feasibility of Dobutamine-Atropine Stress Echocardiography in Patients With Ischemic Left Ventricular Dysfunction

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Abstract

The aim of this study was to analyze whether left ventricular dysfunction affects the safety and feasibility of high-dose dobutamine-atropine stress echocardiography. We examined the results of the test in 318 consecutive patients who were referred for high-dose dobutamine-atropine stress echocardiography and also underwent diagnostic cardiac catheterization. Forty-four patients had a left ventricular ejection fraction of 25% or less (mean, 21%; range, 15% to 25%).

In the entire group of 318 patients, no serious complications (death, myocardial infarction, or ventricular fibrillation) occurred. The overall feasibility of completing the test was excellent (97%). Atrial fibrillation occurred in four patients, nonsustained ventricular tachycardia in 12, and sustained ventricular tachycardia in one. A decrease in systolic blood pressure of greater than 40 mm Hg or a peak systolic pressure of less than 80 mm Hg was present in eight cases. In the group with an ejection fraction of 25% or less, there was a higher rate of significant tachyarrhythmias (14% versus 5%; $p = 0.03$), whereas the feasibility of the test was slightly lower (89%; $p < 0.01$), but no difference for hypotension was found. By multivariate analysis, a history of tachyarrhythmias was the only predictor of stress-induced arrhythmias.

Advanced left ventricular dysfunction does not represent a contra-indication for dobutamine-atropine stress testing.

Introduction

High dose dobutamine-atropine stress echocardiography (DASE) has been shown to be highly feasible and safe and to provide useful diagnostic and prognostic information in patients with suspected or proven coronary artery disease.[1-10] Therefore it has entered the clinical arena for the assessment of stress induced ischemia.

Because there is increasing evidence that coronary revascularization may prolong survival and improve the quality of life in selected patients with left ventricular (LV) dysfunction[11-13] by reducing stress-induced ischemia and improving LV function, the issue of a proper assessment of residual ischemia in these patients is of great clinical relevance.[14]

Pharmacologic stress testing is particularly attractive in these patients, who

often have a reduced exercise capacity. However, few data are available on the feasibility and safety of high-dose dobutamine-atropine stress tests in patients with advanced LV dysfunction.

Accordingly, this study was undertaken to describe the safety profile, hemodynamic response, incidence of stress-induced ischemia, and feasibility of the test in a consecutive group of patients referred for stress testing who also underwent diagnostic cardiac catheterization. The specific objective was to assess how strongly the severity of LV dysfunction affects the safety and feasibility of the test.

Methods

Patients

Between November 1992 and December 1994, 318 consecutive patients with stable proven or suspected coronary artery disease referred for DASE also underwent diagnostic coronary arteriography and LV angiography within 3 months. These 318 patients were included in this study. The patients were derived from 876 patients who underwent DASE at our institution during that period. DASE was performed for evaluation of chest pain, after recent myocardial infarction, or as part of research protocols on myocardial viability. They were included in the study if no unstable angina, active congestive heart failure, significant valvular disease, or protruding thrombus in the left ventricle was present and after informed consent was obtained. There were 244 men and 74 women, aged 31 to 81 years (mean, 58 years). Previous myocardial infarction was present in 239 patients, 84 had a history of heart failure, and 221 had angina. Of 249 patients with no previous coronary bypass grafting, 206 had coronary artery disease: 136 had multivessel disease and 70 had one-vessel disease. A history of ventricular or atrial tachyarrhythmias was present in 24 and 26 cases, respectively. Antianginal medication was continued before the study, including ß-blockers in 127 patients.

Dobutamine-atropine stress echocardiography

A two-dimensional precordial echocardiogram was recorded at baseline, with a commercially available wide-angle phased-array system (Esaote Biomedica SIM 7000 CFM [Esaote, Biomedica, Florence, Italy] or Vingmed CFM 800 [Vingmed

Sound, Horton, Norway]). Standard apical and parasternal views were obtained. DASE was performed as described previously.[4] Briefly, dobutamine was infused through an antecubital cannula starting at a dose of 5 μg/kg/min for 3 minutes, increased with 5 μg/kg for the next 3 minutes, and continued with increases of 10 μg/kg every 3 minutes to a maximum of 40 μg/kg/min. In patients not achieving 85% of their age-predicted maximal heart rate (in men [220 - age] x 85%; in women [200 - age] x 85%) and without signs or symptoms of myocardial ischemia or major adverse effects, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was added intravenously and dobutamine was continued. Thus the maximum dose of pharmacologic agents used in this study was similar to the generally applied protocol at our institution.

Throughout the test the electrocardiogram (three leads) was monitored. A 12-lead electrocardiogram was recorded every minute, whereas blood pressure was measured by sphygmomanometer every 3 minutes. A two-dimensional echocardiogram monitored LV wall motion continuously, obtaining the three standard apical views sometimes together with the short-axis view, and the images were recorded on videotape during the last minute of each stage of the test and continuously after atropine administration. The images were also digitized on-line and subsequently displayed side by side on a quad-screen format, for comparison of baseline and stress images.

The following interruption criteria for the dobutamine-atropine stress test were used: severe chest pain or dyspnea, cardiac arrhythmias with hemodynamic or subjective deterioration, ST segment elevation or horizontal / downsloping ST segment depression greater than 2 mm 80 millisecond after the J point (in the absence of significant ST segment deviation on baseline electrocardiogram), reduction in systolic blood pressure greater than 40 mm Hg compared with baseline, systolic blood pressure less than 80 mm Hg, or any other serious adverse effect during dobutamine infusion. New wall motion abnormalities were considered a reason for interruption in the absence of serious adverse effects only if it was severe and extensive, leading to LV dilation.

To analyze wall motion, the LV wall was divided into 16 segments and each segment was scored on a 4-point scale: 1 = normal wall motion and thickening, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis (absence of systolic wall

motion with thinning). The analysis of the echocardiographic images was performed by two observers, blinded to the clinical data of the individual patient but with knowledge of the doses of dobutamine and atropine used. A wall motion score index (total score divided by the number of segments visualized) at both baseline and peak stress was calculated for each patient. DASE was considered positive for myocardial ischemia when a new wall motion abnormality or a worsening of hypokinesis occurred in one or more segments during stress.[15]

DASE was defined as feasible when symptoms (severe chest pain) or signs (electrocardiographic or echocardiographic) of myocardial ischemia were detected or, in the absence of ischemia, at least the 85% of age-predicted maximal heart rate was achieved.

Cardiac catheterization

The arteriograms were analyzed visually to assess the degree of stenosis of the coronary arterial segments of the three major vessels. Significant stenosis was defined as a diameter stenosis of greater than 50%. The number of vessels with significant lesions was assessed per patient. LV ejection fraction (LVEF) was calculated from volume measurements by single-plane cineangiocardiography according to the area-length method.

Data management

Patients characteristics such as demographic features and medical history, stress test results (adverse effects, hemodynamic response, reasons to stop, and feasibility), and echocardiographic and angiographic findings were loaded into a database at the time of the stress test. Death, myocardial infarction, severe hypotension defined as a drop in systolic pressure of greater than 40 mmHg or a peak systolic blood pressure of less than 80 mmHg, and significant tachy-arrhythmias (supraventricular or ventricular tachycardias, nonsustained or sustained) were defined as end points concerning the safety of the stress test. For further analysis, the patients were also stratified into three groups with LVEF used as a measure of LV function ($\leq 25\%$, $>25\%$ but $\leq 40\%$, or $>40\%$).

Statistical analysis

Univariate analysis of continuous variables, expressed as mean ± SD, was carried out with analysis of variance and Student's *t*-test. Categoric variables were analyzed with the chi-square test or, if necessary, the Fisher exact test. Stepwise logistic regression models were fitted to identify independent predictors of the end points (significant arrhythmias and severe hypotension). The difference in risk was expressed as the odds ratio (OR) with the corresponding 95% confidence intervals (CI). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. To compare and visualize the predictive value of wall motion score index at rest for the end points, we used receiver-operator characteristics curves.

Results

There was no death, myocardial infarction, collapse, or ventricular fibrillation during or shortly after the high-dose dobutamine stress test.
The mean heart rate increased from 71 to 131 beats/min; blood pressure changed from 129/76 to 138/73 mmHg. The maximal double product did not differ significantly between the two groups (18,161 versus 17,786). In 270 tests the maximal dose of dobutamine was administered. Atropine was needed in 69 (36%) of 181 patients not taking ß-blockers and in 76 (60%) of 127 patients taking ß-blockers ($p < 0.0001$).

During the test, ST segment deviation was present in 145 patients, angina in 151 patients, and new or worsened wall motion abnormalities in 194 patients. In 57 patients the angina was severe and reason to interrupt the test. Typical angina always resolved quickly, within 15 minutes of discontinuation of the test or after intravenous ß-blockade was administered. In eight cases dobutamine infusion was discontinued prematurely despite absence of signs or markers of ischemia for the following reasons: maximum atropine dose (n = 6) and hypotension (n = 2). In these patients with a submaximal and nondiagnostic test result, the mean maximal heart rate was 73% (ranging from 67% to 84%), and four were not taking ß-blockers. Thus the overall feasibility of the test was excellent (97%). Fifty of the 57 patients with angina as the interruption criterion had a positive DASE for myocardial ischemia, demonstrating the specificity of the marker chest pain.

Table 1 Clinical and arteriographic data in three groups of patients classified according to LVEF

Data	Group I (n = 44) *n/%*	Group II (n = 78) *n/%*	Group III (n = 196) *n/%*	*p* value
Clinical				
Age (yr) (mean ± SD)	57 ± 8	58 ± 10	59 ± 12	NS
Sex (men)	40/91	68/87	136/69	0.001
History of infarction	44/100	72/92	123/63	<0.001
Previous CABG	17/39	21/27	31/16	<0.005
Angina	25/57	57/73	139/71	NS
Heart failure	38/86	31/40	15/8	<0.001
History of VAR	13/30	7/9	4/2	<0.001
History of AAR	13/30	9/12	4/2	<0.001
Hypertension	17/39	30/39	49/25	<0.05
Diabetes	7/16	16/21	15/8	<0.05
ß-Blockers	7/16	17/22	103/53	<0.001
ACE inhibitors	33/75	44/56	36/18	<0.001
Arteriography *	n = 27	n = 57	n = 165	
No CAD	0	0	43/26	
1 VD	4/15	9/16	57/35	
Multi-VD	23/85	48/84	65/39	

Group I: LVEF of 25% or less, group II: LVEF greater than 25% and 40% or less, group III: LVEF greater than 40%.
NS: not significant, CABG: coronary artery bypass graft, VAR: ventricular tachyarrhythmias, AAR: atrial tachyarrhythmias, ACE: angiotensin-converting enzyme, CAD: coronary artery disease, VD: vessel disease.

* In patients without previous CABG.

Table 2 Comparison of new or worsening wall motion abnormalities, adverse effects, hemodynamic findings, reasons for interruption, and feasibility of the dobutamine test in the three patient groups classified according to LVEF

	Group I (n = 44) *n*/%	Group II (n = 78) *n*/%	Group III (n = 196) *n*/%	*p* value
NWMA	26/59	60/77	108/55	0.004
Adverse effects				
Significant arrhytmias	6/14	4/5	7/4	0.03
Hypotension I	1/2	3/4	4/2	
Hypotension II	4/9	12/15	12/6	} 0.01
Chills	3/7	3/4	7/4	NS
Hypertension	0	0	6/3	NS
Hemodynamic findings				
δ Heart rate (beats/min)	60	62	59	NS
δ Sytolic BP (mm Hg)	5	- 3	14	<0.001
δ Diastolic BP (mm Hg)	- 8	- 9	1	<0.001
Interruption criteria				
Target heart rate	23/52.3	47/60.3	158/80.6	
Angina	10/22.7	19/24.4	28/14.3	
ECG-changes	2/4.5	3/3.8	5/2.6	
NWMA	0	2/2.6	0	
Arrhythmias	2/4.5	0	2/1.0	
Hypotension	1/2.3	3/3.8	2/1.0	
Dyspnea	1/2.3	0	0	
Chills	0	2/2.6	0	
Maximum dose	5/11.4	2/2.6	1/0.5	
Feasibility				
End point reached	39/89	75/96	196/100	<0.01

See Table 1 for group definitions. NWMA: new or worsening wall motion abnormalities, Hypotension I: greater than 40 mm Hg or peak systolic blood pressure less than 80 mm Hg, Hypotension II: 20 to 40 mm Hg, NS: not significant, δ: difference between peak stress and rest, BP: blood pressure, ECG: electrocardiograhy.

The patients were stratified into three groups: 44 in group I with an angiographic LVEF of 25% or less (21% ± 3%), 78 in group II with an LVEF greater than 25% and 40% or less (34% ± 4%), and 196 in group III with an LVEF greater than 40% (61% ± 11%). In Table 1 the clinical and arteriographic data are shown. These data demonstrate that, of the 249 patients with no previous coronary bypass grafting, the distribution of coronary artery disease in the three groups differs, showing lesser prevalence of disease in group III.

The new or worsening wall motion abnormalities, hemodynamic response, adverse effects, and interruption criteria of the test for the three groups are shown in Table 2. The frequency of the use of atropine was not significantly different between the three groups (26 [59%] versus 37 [47%] versus 82 [42%]). The feasibility of the test in all three groups was high, although slightly lower in group I (89% versus 96% versus 100%, $p < 0.01$). In group I, five patients did not achieve the target heart rate despite absence of signs or markers of myocardial ischemia but still reached at least 70% of the age-predicted maximal heart rate. There was no difference in the mean age of patients who did or did not achieve target heart rate.

Significant tachyarrhythmias and hypotension were the two most frequent adverse effects during the stress test. Significant tachyarrhythmias occurred in 17 tests (5%): sustained ventricular tachycardia in one, nonsustained ventricular tachycardia in 12, and paroxysmal atrial fibrillation in four. Arrhythmias were present significantly more often in group I. In three patients ventricular tachycardia was the reason to stop the test prematurely (in all with signs of ischemia). ß-Blockade was needed and used successfully to terminate the arrhythmias in four patients (sustained ventricular tachycardia in one and atrial fibrillation in three). Significant arrhythmias occurred more frequently in patients with a history of heart failure (OR, 4.3; 95% CI, 1.6% to 11.7%), a history of ventricular (OR, 8.4; 95% CI, 2.8% to 25.3%) or atrial tachyarrhythmias (OR, 7.5; 95% CI, 2.5% to 22.4%), and LV dysfunction (LVEF ≤25%: OR, 4.3; 95% CI, 1.4% to 13.4%; wall motion score index >1.6: OR, 3.1; 95% CI, 1.1% to 8.7%), but not in patients with multivessel disease (OR, 0.7; 95% CI, 0.3% to 2.0%). There was no correlation between significant arrhythmias and signs or symptoms of ischemia, the addition of atropine, or the presence of multivessel coronary artery disease.

Table 3 Multivariate analysis for the prediction of tachyarrhythmias according to clinical data and diagnostic findings

	Cardiac arrhythmias during DASE (n = 17)(*n*)	No cardiac arrhythmias during DASE (n = 301)(*n*)	OR	95% CI
Previous AAR	6	20	5.5	1.6 - 17.8
Previous VAR	6	18	6.2	1.9 - 20.1

AAR: atrial arrhythmias, VAR: ventricular arrhythmias.

Multivariate analysis showed an independent correlation with a history of atrial and ventricular arrhythmias but not with LV dysfunction (Table 3). Hypotension of more than 20 mm Hg occurred during 30 tests but was severe (>40 mm Hg or peak systolic blood pressure <80 mm Hg) in only eight. Hypotension was present more frequently in the groups with a reduced LV function. Small but significant differences in blood pressure response between the three groups occurred during the test.

There was no significant correlation between the occurrence of severe hypotension and clinical data, extent of coronary artery disease, or stress test results, nor with the addition of atropine or the severity of LV dysfunction.

Discussion

The specific aims of this study were to assess whether LV dysfunction enables clinicians to perform a "complete" DASE test or is associated with a higher complication rate compared with such tests in patients with a normal or moderately reduced LV function. Ventricular and supraventricular tachyarrhythmias, as well as hypotension, have been reported as the most worrisome adverse effects of a dobutamine stress test;[6,7,16] however, few data are available in patients with advanced LV dysfunction.[17]

Safety of DASE

The initial hypothesis was that there could be an increased risk to induce ischemic changes with high-dose dobutamine and atropine in patients with severely reduced LVEF and that the test would be potentially dangerous in these patients. Despite our aggressive approach, with atropine used in addition to dobutamine, our results reject the initial hypothesis. Although frequently myocardial ischemia was induced, there was no major complication during DASE such as death, myocardial infarction, or ventricular fibrillation.

A decrease in systolic blood pressure decrease of 20 mm Hg or greater but less than 40 mm Hg during the test has not been considered by us to be a serious adverse effect, in contrast to others.[7,16,18] Significant tachyarrhythmias were infrequent (5%), similar to that found by others;[6,7,16] only in four patients were intravenous ß-blockers needed to restore sinus rhythm. Our study shows that a history of atrial or ventricular tachyarrhythmias but not LV (dys)function is independently correlated with the occurrence of significant tachyarrhythmias. In a previous study we reported that LV dysfunction is a risk factor for paroxysmal tachyarrhythmias.[6] However, the number of patients with advanced LV dysfunction was small. This study includes a new study population with a broad range of LV dysfunction, all with measurement of angiographic LVEF. This strengthens our conclusion that LV function does not influence the occurrence of cardiac arrhythmias, not even in a patient population with extensive LV dysfunction after an aggressive dobutamine-atropine protocol. Furthermore, we confirm that, although atropine by withdrawal of parasympathetic tone may increase the risk of significant cardiac arrhythmias, the addition of atropine does not actually increase the occurrence of arrhythmias.[5-7] The strong correlation between dobutamine stress-induced cardiac arrhythmias and a history of arrhythmias in itself is not surprising and confirms previous reports.[6]

Hypotension has been considered a reason for termination of the test only if symptoms or severe (>40 mm Hg) hypotension occurred. This happened in eight cases, in two accompanied by sinus bradycardia. The occurrence rate of severe hypotension was infrequent and similar in the groups with different LVEF. It was not related to the occurrence of new wall motion abnormalities or other markers of ischemia. These data are consistent with those we found previously in

a larger group of patients with less advanced LV dysfunction.[6] Vasodepressor reflex mechanisms induced by vigorous myocardial contractions, dynamic intraventricular outflow obstruction, or the vasodilator effects of dobutamine are possible mechanisms of dobutamine-induced hypotension.[19,20] Other adverse effects, such as chills, hypertension, or dyspnea, were minor and present infrequently. They seldom were the cause of termination of the test.

Feasibility of DASE

The criteria for interruption of the test were similar in the different groups. We rarely considered the appearance of new wall motion abnormalities in the absence of symptoms or hemodynamic deterioration as an interruption criterion. Despite the more frequent use of ß-blockers, the test could be completed (reaching the end points of ischemia or target heart rate) in a high proportion of patients with normal and mildly reduced LV function (Table 2). The frequency of the use of atropine in addition to dobutamine was similar in the three groups with different severities of LV dysfunction. The slightly lower feasibility of the test in the group with advanced LV dysfunction can be explained by a lower maximal (but at least 70% was reached) heart rate reached in the absence of signs or symptoms of myocardial ischemia.

Our definition of a submaximal nondiagnostic test is rather arbitrary. One could argue that because nearly all patients in group I reached 75% of the target heart rate, the feasibility in this group with predominance of multivessel disease was excellent. A possible explanation for the lower increase in heart rate in group I is the down-regulation of the cardiac ß-receptors that has been described in patients with advanced LV dysfunction.[21]

In conclusion, in advanced ischemic LV dysfunction, high-dose DASE is feasible and diagnostic in a high proportion of patients and does not represent a risk factor for serious complications or adverse effects. A history of significant arrhythmias represents an increased risk for the occurrence of arrhythmias during the test.

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Part II

RECOVERY OF CONTRACTILE FUNCTION

Chapter 5

Prediction of Improvement of Ventricular Function After First Acute Myocardial Infarction Using Low-Dose Dobutamine Stress Echocardiography

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Abstract

This study was performed to assess the prevalence of spontaneous improvement of regional left ventricular dysfunction in patients after acute myocardial infarction, and to evaluate the role of low-dose dobutamine stress echocardiography for its prediction.

In 57 patients with a first acute myocardial infarction (thrombolysis, n = 27; Q-wave, n = 49), regional wall motion was evaluated with two-dimensional echocardiography at rest, during a low-dose dobutamine stress test performed within 1 week after hospital admission, and at 3-month follow-up.

Myocardial viability was considered if there was an improvement of ≥ 1 grade in dyssynergic segments from rest to low-dose dobutamine infusion; recovery of regional function was defined as an improvement of ≥ 1 grade between rest and follow-up echocardiograms. Wall motion score index decreased from rest to low-dose dobutamine echocardiography (1.46 ± 0.29 to 1.39 ± 0.30, $p < 0.0001$), and this change persisted at follow-up study (1.37 ± 0.30). No differences were found between patients who did and did not undergo thrombolysis, or between those who had Q-wave and non-Q-wave infarction. At baseline echocardiography, 189 of 627 segments were dyssynergic (85 hypokinetic, 104 akinetic). Viability at low-dose dobutamine stress echocardiography was more frequent in hypokinetic than in akinetic segments (30 of 85 versus 12 of 104, odds ratio 4.18, 95% confidence interval [CI] 1.87 to 9.48). Spontaneous recovery was more frequent in hypokinetic than in akinetic segments (30 of 85 versus 20 of 104, odds ratio 2.29, CI 1.13 to 4.68). Sensitivity, specificity, and positive and negative predictive values of low-dose dobutamine stress echocardiography for predicting late recovery of regional function were 66%, 94%, 79%, and 88%, respectively. Sensitivity was lower in akinetic segments than in hypokinetic segments (35%, CI 0.14 to 0.56, versus 87%, CI 0.75 to 0.99). An improvement during low-dose dobutamine stress echocardiography was a strong predictor of reversible postischemic dysfunction (odds ratio 17.1, CI 3.5 to 97.1).

In conclusion, in patients after a first, relatively uncomplicated acute myocardial infarction, late spontaneous recovery occurs in 26% of the dyssynergic segments. Low-dose dobutamine stress echocardiography provides very specific information for predicting lack of improvement and has a high sensitivity for

predicting improvement in hypokinetic segments, but is not useful in identifying akinetic segments that will spontaneously improve.

Introduction

Myocardial stunning is defined as transient prolonged postischemic dysfunction that may occur after the restoration of normal coronary flow.[1] It has been observed in several clinical conditions, including in patients after acute myocardial infarction treated with thrombolysis.[2-5] The natural history in patients with acute myocardial infarction not treated with thrombolysis includes potential improvement in left ventricular function at follow-up.[6] If this is true, the evaluation of viable myocardium should be desirable in all patients early after an acute myocardial infarction, and could influence the choice between medical treatment or coronary revascularization in selected patients. With the combined analysis of flow and metabolism, positron emission tomography is the reference noninvasive method for assessing the presence of viable myocardium.[7]

Recently, myocardial perfusion scintigraphy with different isotopes and with different protocols has been proposed for the same purpose.[8] The administration of dobutamine in conjunction with echocardiographic wall motion analysis has been proposed as a simpler alternative to the more sophisticated and expensive nuclear techniques.[9-12] Despite interest in these findings, little is known about the spontaneous recovery of segmental left ventricular function and the potential role of low-dose dobutamine stress echocardiography for its prediction.

Accordingly, the aims of this study were to assess the incidence of late (3 months) spontaneous improvement of regional left ventricular function in an unselected series of patients after a first acute myocardial infarction, and to evaluate the potential role of low-dose dobutamine stress echocardiography (performed within 1 week after myocardial infarction) for its prediction.

Methods

Patient group

Fifty-seven consecutive patients (48 men and 9 women, mean age 58 ± 10 years, range 25 to 76) were prospectively enrolled in this study. Criteria for recruitment were: 1) admission at our institutions with a diagnosis of first acute

myocardial infarction (prolonged chest pain, ≥1mm ST-segment deviation in ≥ 2 leads on the initial electrocardiogram, and typical creatine kinase-MB isoenzyme pattern); and 2) wall motion abnormalities on a resting echocardiogram performed within 7 days of admission. Patients with valvular heart disease (n = 2), prior myocardial infarction (n = 4), previous coronary artery bypass graft or percutaneous transluminal coronary angioplasty (n = 3), postinfarction angina requiring revascularization procedures (n = 3), or infarction complicated by severe hemodynamic instability (n = 2) were excluded. No patient was excluded because of inadequate echocardiogram. Twenty-seven patients were treated with thrombolytic agents within 6 hours from the beginning of symptoms, and 30 had contraindications or late presentation to the hospital. Eight patients had a non-Q-wave myocardial infarction, and 2 of them underwent thrombolytic therapy. The site of myocardial infarction was anterior in 30 patients and inferior and/or lateral in 27.

Predischarge dobutamine stress echocardiography and follow-up study

After giving verbal informed consent, all patients underwent dobutamine stress echocardiogram within 7 days after hospital admission. Antianginal drugs, digitalis and other drugs that might alter myocardial contractility were withdrawn 24 to 48 hours before the test. Dobutamine was infused by a volumetric pump at incremental doses according to a protocol based on 2 stages of 5 and 10 μg/kg/min (5 min/dose) and 3-minute stages of 20, 30, and 40 μg/kg/min, plus the addition of atropine (0.25 to 1 mg) in patients not achieving 85% of their age-predicted maximal heart rate who had no symptoms or signs of ischemia. The first 2 stages were considered a "low-dose stress test" and were evaluated for the presence of viable myocardium. Throughout the dobutamine infusion, an electrocardiogram lead was continuously monitored on the echocardiographic monitor. Twelve-lead electrocardiograms and blood pressures were recorded at rest and at the end of each stage. A two-dimensional echocardiogram was monitored throughout the test and recorded on videotape at rest and during the last minute of each stage. The test was stopped in case of severe new wall motion abnormalities, typical angina, significant cardiac arrhythmias, or any other limiting side effects.

At 3-month follow-up, two-dimensional echocardiograms were obtained at rest in all patients after adequate pharmacologic washout. Echocardiograms were

recorded on videotape for subsequent analysis and comparison with the previous examination. All echocardiograms were reviewed on the videotapes and a consensus was achieved by 2 observers unaware of the clinical data. For the purposes of this study, the left ventricular wall was divided into 11 segments.[13] Both inward wall motion and wall thickening were evaluated, and each segment was graded as 1 = normal or hyperkinetic, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. Baseline images before dobutamine infusion were used as references and compared with the corresponding images during low-dose dobutamine infusion. An improvement of ≥ 1 grade in the dyssynergic segments during dobutamine infusion was considered as a marker of viable myocardium. Thus, hypokinetic segments returning to normal, and systolic myocardial thickening becoming apparent in a segment that was either akinetic or dyskinetic were considered as a positive test for the presence of viable myocardium. Follow-up echocardiograms were compared with the corresponding rest images before dobutamine infusion for comparative segmental analysis. For each segment, a recovery of function was defined as an improvement of ≥ 1 grade. For each study, a wall motion score index was calculated, dividing the sum of the scores by the number of the segments. Because hyperdynamic left ventricular segments during low-dose dobutamine stress echocardiography were scored as normal (1), wall motion score index was affected only by abnormally contracting segments.

Statistical analysis

Continuous data are expressed as mean $\pm$ SD. Continuous variables were analyzed using analysis of variance for repeated measurements and paired *t* test with the Bonferroni correction. An unpaired *t* test was used when appropriate. Sensitivity, specificity, and positive and negative predictive values rely on the standard definition and are reported with the corresponding 95% confidence interval (CI). The difference in late recovery was expressed as the odds ratio with the corresponding CI. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

Results

The median interval from myocardial infarction to dobutamine test was 4

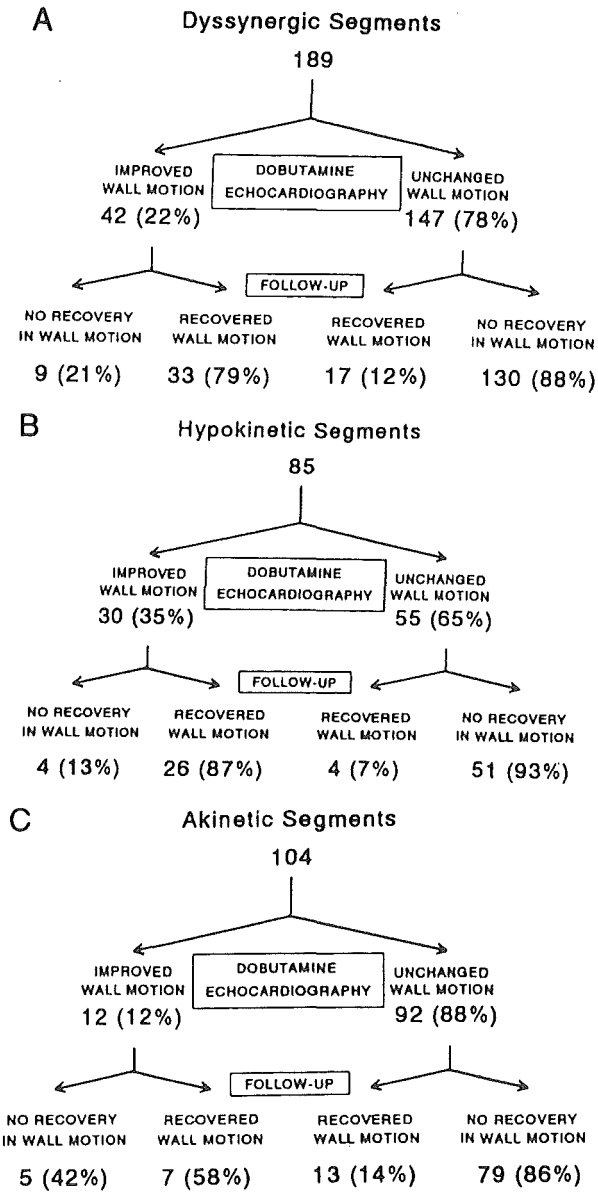

Figure 1 Response of the segments to low-dose dobutamine stress echocardiography and the results at follow-up, for all the dyssynergic segments (*A*), including only hypokinetic (*B*) or akinetic (*C*) segments.

days (range 3 to 7). Atropine was added to dobutamine in 35 patients. No complications occurred during the dobutamine stress test. Heart rate and systolic blood pressure were 80 ± 19 beats/min and 143 ± 38 mm Hg at rest and 82 ± 20 beats/min and 143 ± 38 mm Hg after low-dose of dobutamine infusion.

Nineteen patients (33%) had a positive low-dose dobutamine stress echocardiogram, and 16 of these (84%) had recovery of at least 1 segment at follow-up, whereas 29 of the 38 patients (76%) with a negative low-dose dobutamine stress echocardiogram had no improvement (n = 28) or even a worsening (n = 1) at follow-up.

There was a significant reduction in wall motion score index between rest and both low-dose dobutamine infusion and follow-up echocardiograms (1.46 ± 0.29 versus 1.39 ± 0.30 versus 1.37 ± 0.30, $p < 0.0001$). Patients did not differ according to the type of treatment (thrombolysis versus no thrombolysis) or the type of infarction (Q-wave versus non-Q wave).

Analysis of segments

At baseline, 189 of 627 segments were dyssynergic (30%). Eighty-five of them were hypokinetic and 104 akinetic. Low-dose dobutamine stress echocardiography revealed the presence of viable myocardium in 42 of 189 segments (22%). At baseline, 30 of these were hypokinetic and 12 were akinetic (7 became hypokinetic, 5 normal). Thus, viability was detected more frequently in hypokinetic than in akinetic segments (35% versus 12%, odds ratio 4.18, CI 1.87 to 9.48). At follow-up, 50 of 189 segments (26%) recovered: 10 from akinetic to normal, 10 from akinetic to hypokinetic, and 30 from hypokinetic to normal. Recovery occurred in 33 of 42 segments (79%) that improved with low-dose dobutamine stress echocardiography, and in only 17 of 147 (12%) that did not improve. Recovery was more frequent in hypokinetic than in akinetic segments (35% versus 19%, odds ratio 2.29, CI 1.13 to 4.68) (Figure 1).

When considering only the "viable" segments at low-dose dobutamine stress echocardiography, there was a trend toward more frequent late recovery in the hypokinetic than in the akinetic segments (87% versus 58%, odds ratio 4.64, CI 0.78 to 29.55). Sensitivities, specificities, and predictive values of low-dose dobutamine stress echocardiography for the prediction of spontaneous recovery at

Table 1 Prediction of recovery of dyssynergic segments using dobutamine stress echocardiography

	Sens	Spec	PPV	NPV
All dyssynergic segments (n = 189)	66% (0.53-0.79)	94% (0.89-0.97)	79% (0.66-0.92)	88% (0.83-0.93)
Akinetic segments (n = 104)	35% (0.14-0.56)	94% (0.89-0.99)	58% (0.30-0.86)	86% (0.79-0.93)
Hypokinetic segments (n = 85)	87% (0.75-0.99)	93% (0.86-1.0)	87% (0.75-0.99)	93% (0.86-1.0)

Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value.
Values in parentheses are the 95% confidence interval.

follow-up are reported in Table I, both for the overall group and according to the different degrees of dyssynergy.

Predictors of spontaneous recovery

Improvement in wall motion during low-dose dobutamine stress echocardiography (odds ratio 17.1, CI 3.5 to 97.1) and hypokinesia at rest (odds ratio 2.29, CI 1.13 to 4.68) were the only indicators of reversible postischemic dysfunction after acute myocardial infarction.

Discussion

To our knowledge, this is the first study in which patients with a first, relatively uncomplicated acute myocardial infarction were evaluated by dobutamine stress echocardiography and followed up to observe the spontaneous recovery of function, independent of the treatment with thrombolytic agents. Moreover, the potential confounding effects of the antianginal therapy were avoided. Thus, we attempted to describe the natural history of dyssynergic segments.

The main findings of the present study can be summarized as follows:
1) Approximately one fourth of the dyssynergic segments after acute myocardial infarction show a spontaneous recovery at 3-month follow-up.
2) The incidence of the recovery is higher in hypokinetic than in akinetic segments.
3) Low-dose dobutamine stress echocardiography is very specific for predicting the lack of improvement in segmental left ventricular function (94%).
4) The sensitivity is high (87%) in hypokinetic segments, and lowest (35%) in akinetic segments.

Among the affected left ventricular segments in our population, the prevalence of akinesia and hypokinesia was similar (55% versus 45%, respectively). However, improvement during the low-dose dobutamine stress test and late spontaneous recovery occurred more frequently in the hypokinetic segments. This is not surprising, since it seems logical to hypothesize that hypokinetic segments contain a mixture of scar, normal, and viable myocardium, whereas in the akinetic segments the amount of scar is predominant. The time course of recovery of the hypokinetic segments demonstrates that in one third of the cases, the dysfunction was probably based on the presence of myocardial stunning. This phenomenon is less frequent when akinetic segments are considered. Among the segments that were viable during low-dose dobutamine stress echocardiography, there was a clear trend toward less frequent spontaneous recovery in akinetic than in hypokinetic segments (58% versus 87%). It is conceivable that some of these akinetic segments sustain incomplete reperfusion, resulting in a combination of myocardial stunning and hibernation, with less chance of spontaneous recovery.

The comparative role of low-dose dobutamine stress echocardiography and positron emission tomography for detecting viable myocardium was first assessed by Pierard et al.[10] Viability was found in 10 patients with acute anterior myocardial infarction, and recovery occurred in 6 of them; patients with no viable myocardium detected by echocardiography had no functional recovery at follow-up. Patients in whom echocardiography revealed viable myocardium but who did not have late functional recovery were characterized by an abnormally high glucose-to-perfusion ratio, suggesting jeopardized myocardium and persistent ischemia. This pattern may explain our finding of absence of recovery in some segments that showed "viability" with low-dose dobutamine stress echocardiography.

The role of low-dose dobutamine stress echocardiography for identifying viable myocardium and predicting improvement after coronary revascularization (either with percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) was assessed by Barilla et al.[12] In this study, 21 patients with anterior non-Q-wave myocardial infarction or post-thrombolytic therapy, or both, were evaluated. Wall motion improved during dobutamine stress echocardiography in all but 1 patient, as indicated by a reduction in wall motion score index. At follow-up, all patients had an improvement in contractility, although the magnitude was greater in the 13 patients who underwent revascularization. Recently, Smart et al[11] investigated the role of different indicators of reversible postischemic dysfunction (wall motion at different doses of dobutamine, non-Q-wave myocardial infarction, peak creatine kinase) in 51 patients after thrombolytic therapy. Low-dose dobutamine stress echocardiography had a sensitivity of 86% and a specificity of 90% for reversible dysfunction, and was sensitive in all infarct locations. Of the other variables not related to stress echocardiography, non-Q-wave myocardial infarction was sensitive only in anterior infarction. However, in that study, 22 patients underwent revascularization before hospital discharge on the basis of angiographic findings alone, and this can affect the real assessment of myocardial stunning. Although these data indicate that low-dose dobutamine-induced wall motion improvement may be sensitive for reversible postischemic dysfunction, all these studies focused on patients after thrombolytic therapy, often limited to anterior myocardial infarction; furthermore, the role of revascularization is difficult to evaluate, and the relative importance of the pattern of dyssynergy at rest has not been considered.

Study limitations

Several limitations of the present study deserve further consideration. Coronary arteriography was not performed in our patients on a routine basis and neither positron emission tomographic scanning for metabolic activity nor thallium scintigraphy was performed. However, we believe that the reference method for stunned myocardium should be spontaneous recovery of wall motion as we have evaluated.

Echocardiograms were evaluated qualitatively and digital cineloop systems

were not used. In a previous study using dobutamine stress echocardiography, digital techniques did not offer advantages over analysis on videotapes in terms of diagnosis of myocardial ischemia.[14]

Changes in regional wall motion, and particularly hypokinetic segments becoming normal, are subtle and difficult to evaluate. Dobutamine stress echocardiography was performed within 7 days hospital admission. Thus, some segments could have already recovered, lowering the prevalence of a positive low-dose dobutamine stress echocardiogram.

Finally, the results of this study cannot be extrapolated to patients with complicated acute myocardial infarction, who represent the ideal target population and for whom proper identification of myocardial viability is clinically most relevant.

Acknowledgements

We are indebted to all nurses working at our institutions for assistance in performing the echocardiographic studies.

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Chapter 6

T-wave Normalization During Dobutamine Echocardiography for Diagnosis of Viable Myocardium

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Introduction

Low-dose dobutamine stress echocardiography has been proposed as a useful tool for assessing reversible dysfunction after myocardial infarction.[1,2] However, subtle regional wall motion improvement during low-dose dobutamine infusion can be difficult to evaluate, especially in akinetic segments.[3] In our experience with dobutamine stress testing in postinfarction patients, we frequently observed the occurrence of T-wave normalization with low-dose dobutamine without signs of myocardial ischemia. Because we were puzzled by this electrocardiographic (ECG) finding, we wondered whether this pattern could reflect the presence of reversible mechanical dysfunction. In particular, we wanted to test the hypothesis that normalization of inverted T wave during low-dose dobutamine infusion represents a sign of dysfunctioning but still viable myocardium in patients after recent myocardial infarction.

Methods

With this aim in mind, we enrolled in a prospective study 90 consecutive patients admitted to our institutions who fulfilled the following admission criteria: 1) first Q-wave myocardial infarction (as documented by history, typical isoenzymes curves, and ECG changes), 2) negative T waves in ≥ 2 infarct-related ECG leads, and 3) segmental wall motion abnormalities on the resting echocardiogram. Patients with overt heart failure and early postinfarction angina requiring revascularization were excluded. Fifty patients were treated with thrombolytic agents. The ECG location of the infarction was anterior in 39 and inferior and/or lateral in 51 patients.

Low-dose dobutamine stress echocardiography (5 and 10 μg/kg/min, each stage lasting 5 minutes) was performed within 7 days after hospital admission, with adequate withdrawal of all antianginal and other cardioactive drugs. Regional wall motion was evaluated on a 11-segment 4-grade scale, where 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. Any improvement in wall motion during low-dose dobutamine infusion in ≥ 1 segment already dyssynergic at rest was considered positive for the presence of viable myocardium. A wall motion score index was derived by dividing the sum of the individual scores by the number of the segments. A 12-lead electrocardiogram was recorded at rest and

every minute during the test. T-wave normalization was defined as negative T waves becoming upright in ≥2 infarct-related ECG leads during dobutamine infusion. Both echocardiograms and electrocardiograms were reviewed and a consensus reached by 2 observers unaware of the results of the other test. In 59 patients a rest echocardiogram was obtained after 3 months. During this period, no cardiac events (unstable angina, myocardial infarction, revascularization procedure) occurred. Late spontaneous recovery of function was defined as any improvement of wall motion in the infarct area from predobutamine to follow-up echocardiograms.

Statistical analysis

The agreement between echocardiography and electrocardiography was defined as the percentage of concordant diagnosis, and it was also assessed by calculating the kappa (K) value and its standard error; K values between 0.50 and 0.75 were considered indicative of good agreement. Sensitivity, specificity, accuracy, and positive and negative predictive values of both echocardiography and electrocardiography for predicting late spontaneous recovery of function relied on standard definitions, and their values were expressed as percentage with 95% confidence intervals.

Results

All patients completed low-dose dobutamine stress testing without adverse effects. Both heart rate and systolic blood pressure were similar at rest and at low-dose dobutamine infusion (76 ± 18 versus 78 ± 18 beats/min; 140 ± 36 versus 140 ± 36 mmHg, respectively). Improvement in wall motion in the infarct area during dobutamine infusion occurred in 29 patients (32%), while the T wave normalized in 23 (26%). An example of T-wave normalization during dobutamine infusion is shown in Figure 1. The overall agreement between echocardiography and electrocardiography was 82% (K = 0.57) (Figure 2).

Patients with improvement in wall motion and T-wave normalization (group 1, n = 18) were compared with those with improvement in wall motion but no change in the negative T waves (group 2, n = 11). In these 2 subgroups, both the number of dyssynergic segments at rest and the changes in wall motion score index

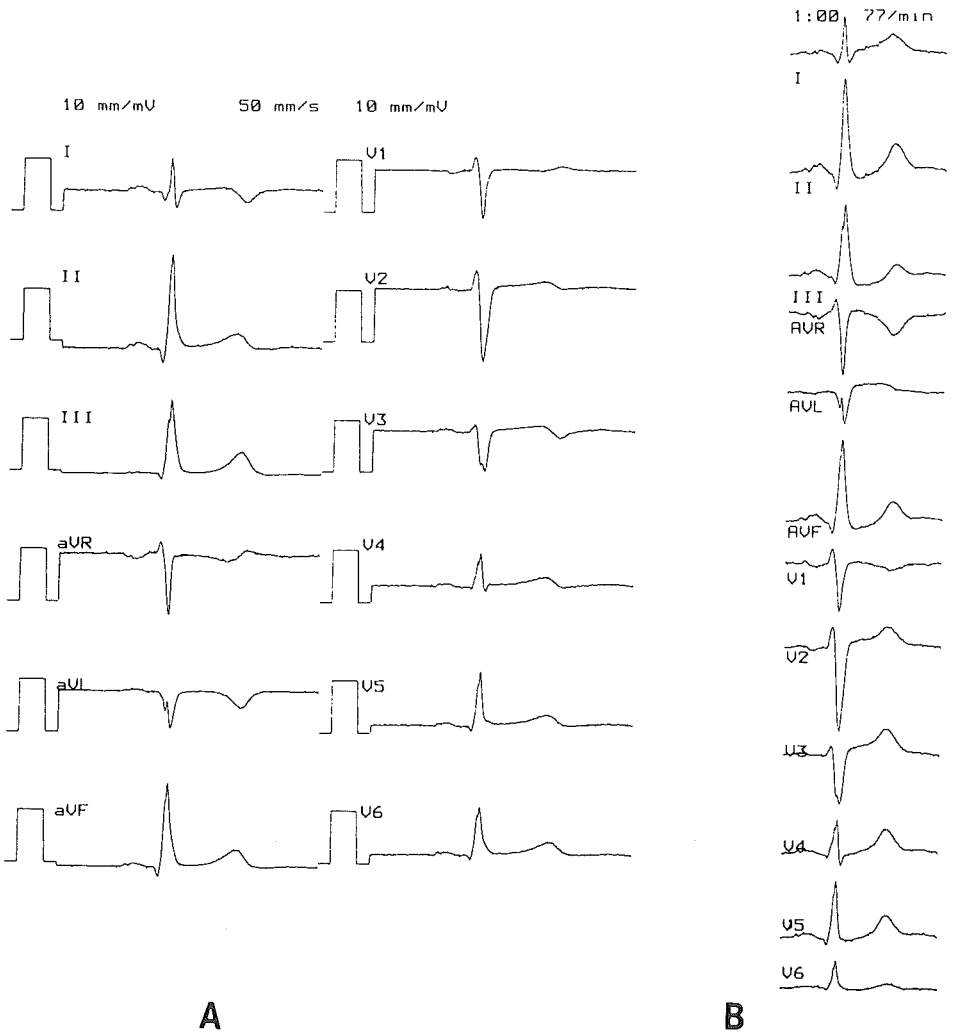

Figure 1 Twelve-lead electrocardiogram at rest (A) and during low-dose dobutamine infusion (B) in a patient with lateral Q-wave myocardial infarction. Negative T waves at rest in leads I and aVL normalize during inotropic stimulation.

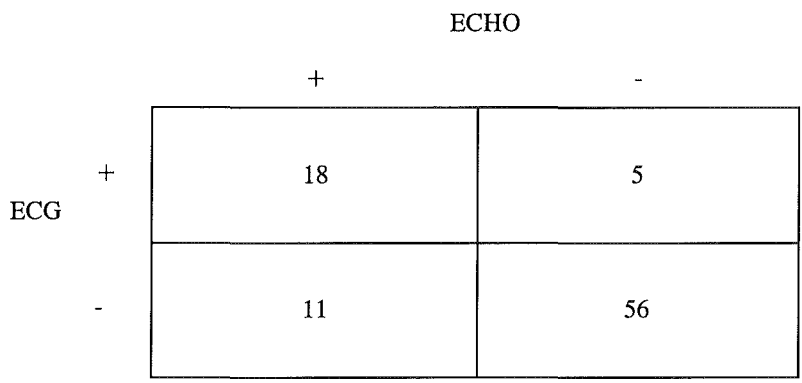

Figure 2 Agreement between improvement in contractility (ECHO +) and T- wave normalization (ECG +) during low-dose dobutamine stress testing in the original group of 90 patients.
ECG: electrocardiography, ECHO: echocardiography.

during low-dose dobutamine infusion were similar. However, the percentage of resting dyssynergic segments that improved during low-dose dobutamine infusion was higher in patients with T-wave normalization (Table 1). At follow-up, spontaneous recovery in the infarct area was present in 21 of 59 patients (36%). In these 21 patients, agreement between echocardiography and electrocardiography was 62%. Echocardiography and electrocardiography had similar values of sensitivity, specificity, accuracy, and positive and negative predictive values for predicting late spontaneous recovery of function. When either improvement in wall motion or T-wave normalization was considered, there was a trend toward higher sensitivity, without loss of specificity (Table 2).

Discussion

In recent years there has been an increasing interest in the detection of viable myocardium. Inotropic challenge with low-dose dobutamine infusion has the potential to recruit the contractile reserve of dysfunctioning but still viable myocardium which can be recognized by two-dimensional echocardiography. The results of this approach are encouraging, both for stunned and hibernating

Table 1 Resting dyssynergies and improvement in wall motion in 29 patients with positive results on low-dose dobutamine echocardiography

	Group 1 (n = 18) *	Group 2 (n = 11) !
Mean no. of dyssynergic segments (95% CI)	3.1 (1.9-4.3)	3.5 (2.3-4.8)
Mean no. of dyssynergic segments improving with LDD (95% CI)	2.2 (1.6-2.8)	1.7 (1.3-2.2)
% of dyssynergic segments improving with LDD (95% CI)	84 (73-95)	58 (37-78)
Mean WMSI at rest (95% CI)	1.58 (1.34-1.81)	1.71 (1.44-1.99)
Mean WMSI at LDD (95% CI)	1.32 (1.12-1.51)	1.44 (1.18-1.70)
Mean changes in WMSI from rest to LDD (95% CI)	0.26 (0.19-0.33)	0.27 (0.18-0.35)

CI: confidence interval, LDD: low-dose dobutamine infusion, WMSI: wall motion score index.

* Patients with T-wave normalization during low-dose dobutamine infusion.

! Patients with persistent negative T waves during low-dose dobutamine infusion.

myocardium. However, the prevalence of this phenomenon as evaluated in previous studies by low-dose dobutamine stress echocardiography is different.[1-4] This may be due to the difficult and subjective evaluation of subtle changes in segmental wall motion and thickening during dobutamine infusion. Furthermore, wall motion can be also affected by factors not primarily related to the inotropic state. Thus, evaluation of other nonechocardiographic parameters may be helpful for identifying viable myocardium during low-dose dobutamine infusion.

The underlying pathophysiology of negative T waves in ischemic heart disease is not completely understood. There is clinical evidence that T-wave inversion is associated with viable myocardium in patients with unstable angina, being an electrophysiological correlate of myocardial stunning.[5] In this clinical

Table 2 Relative value of echocardiography and electrocardiography during dobutamine stress testing for predicting late spontaneous recovery of function after acute myocardial infarction

	Sensitivity	Specificity	Accuracy	PPV	NPV
Echo *	57 (34-78)	89 (75-97)	78 (65-87)	75 (47-92)	79 (64-90)
ECG !	47 (25-70)	92 (78-98)	76 (63-86)	76 (46-95)	76 (61-87)
Echo and/or ECG	71 (45-88)	89 (75-97)	83 (71-91)	79 (54-94)	85 (70-94)

Echo: echocardiography; ECG: electrocardiography, NPV: negative predictive value, PPV: positive predictive value.

* Improvement in contractility during low-dose dobutamine stress testing.

! Normalization of negative T waves during low-dose dobutamine stress testing.

Values are expressed as percentage with corresponding 95% confidence intervals.

setting, negative T waves reflect primary changes due to an abnormal pathway of electrical repolarization. In Q-wave myocardial infarction, negative T waves in the infarct ECG leads may result from change in the order of repolarization secondary to alterations of the sequence of depolarization. However, experimental and clinical data indicate that sympathetic denervation of viable myocardium distal to the area of necrosis also may delay repolarization and result in primary negative T waves.[6] In patients with recent myocardial infarction, inotropic stimulation with low-dose dobutamine may have the potential to normalize primary T-wave changes (unmasking the presence of viable myocardium), while secondary T-wave changes are not affected.

The results of the present study indicate a good agreement between improvement in wall motion and normalization of negative T waves during low-dose dobutamine infusion. We have also found that, conditional to patients with positive results on low-dose dobutamine stress echocardiography, the percentage of dyssynergic segments improving during dobutamine infusion was higher in those with a concomitant T-wave normalization. However, and most interesting, 5

patients with negative results on low-dose dobutamine echocardiography had T-wave normalization as well, with late spontaneous improvement in wall motion in all 3 who were evaluated at follow-up. Thus, the main finding of the present study is the additional value of this ECG pattern for predicting late spontaneous recovery of segmental wall motion. The higher sensitivity of electrocardiography added to echocardiography compared with that of echocardiography alone was not corroborated by a clear separation of the corresponding 95% confidence intervals. However, from this figure we estimated that $\approx$ 1,000 patients should be needed to reach a statistical significance. The results of the present study may also explain the low specificity for myocardial ischemia of normalization of negative T waves during exercise reported in previous studies.[7] This finding may represent viable myocardium not at risk. Finally, the relatively low sensitivity for predicting recovery with low-dose dobutamine echocardiography in our study compared with available data[1] can be explained by several factors: the different patients selected, the different echocardiographic left ventricular model and definition of improved wall motion and reversible dysfunction, and the prevalence of akinetic segments at rest, which has been shown to lower sensitivity of the test.[3]

In conclusion, these preliminary data indicate that T-wave normalization during low-dose dobutamine stress testing is an ancillary sign of viable myocardium after acute myocardial infarction and increases the sensitivity of echocardiography for predicting late spontaneous recovery of function.

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We thank all nurses working at our institutions for their assistance and expertise in performing the stress echocardiographic studies.

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Chapter 7

Prediction of Improvement of Regional Left Ventricular Function After Surgical Revascularization

A Comparison of Low-Dose Dobutamine Echocardiography With ^{201}TI Single-Photon Emission Computed Tomography

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Abstract

Background

Although both ^{201}Thallium (^{201}Tl) scintigraphy and low-dose dobutamine echocardiography (LDDE) have been proposed as effective methods of assessing myocardial viability, their relative efficacies are unknown. The aim of the present study was to compare the two imaging techniques in the prediction of improvement of regional left ventricular (LV) function after surgical revascularization.

Methods and Results

Thirty-eight patients with severe chronic LV dysfunction (ejection fraction $\leq 40\%$, one or more akinetic (Ak) or severely hypokinetic (SH) segments on resting echocardiogram) who underwent uncomplicated coronary artery bypass graft surgery were studied with simultaneous dobutamine stress echocardiography and poststress reinjection ^{201}Tl single-photon emission computed tomography (SPECT) before surgery. The Ak or SH segments were considered viable by LDDE when wall thickening improved during the infusion of 10 $\mu g.kg^{-1}.\ min^{-1}$ dobutamine. Scintigraphic definition of viability was the presence of normal ^{210}Tl uptake, totally reversible defect, partially reversible defect, or moderately severe fixed defect. The postoperative improvement of dyssynergic segments was determined with a rest echocardiogram 3 months after surgery.

Of 608 LV segments, 169 were classified as Ak and 51 as SH on resting preoperative echocardiography. Of these, 170 were successfully revascularized. Wall motion during LDDE improved in 33 severely dyssynergic segments and was more frequent in SH than in Ak segments (19 of 44 versus 14 of 126, $p < 0.0001$). Viability was detected by ^{201}Tl SPECT criteria in 103 SH or Ak segments. Thirty-two of the 33 segments from LDDE responders were judged viable on ^{201}Tl SPECT, whereas ^{201}Tl viability was also detected in 71 of 137 segments from LDDE nonresponders.

The sensitivity and the specificity for the prediction of postoperative improvement of segmental wall motion were 74% (95% confidence interval [CI], 67% to 81%) and 96% (95% CI, 93% to 99%) by LDDE, and 89% (95% CI, 84% to 94%) and 48% (95% CI, 40% to 56%) by ^{201}Tl SPECT, respectively. Positive predictive value of LDDE was higher than that of ^{201}Tl SPECT (85%,

[95% CI, 80% to 90%] versus 33% [95% CI, 26% to 40%]).

Thirty-six patients had angina before and only 1 had angina 3 months after revascularization. High-dose dobutamine echocardiography demonstrated significant reduction in stress-induced ischemia (new or worsening of preexisting wall motion abnormalities) after surgery (from 163 to 23 LV segments).

Conclusions

In patients with severe chronic LV dysfunction, LDDE is a good predictor of the improvement of dyssynergic segments after revascularization. Because ^{201}Tl SPECT overestimates the probability of postoperative improvement of dyssynergic segments, LDDE should be the preferred imaging technique for preoperative assessment of these patients.

Introduction

Coronary artery bypass graft surgery can improve regional and global ventricular performance and the functional status of patients with chronic left ventricular (LV) dysfunction.[1] The concepts of stunned and hibernating myocardium have been advocated to explain such improvement.[2,3] Reliable preoperative prediction of patients in whom regional and/or global LV dysfunction will improve after revascularization would present several clinical advantages, including the appropriate referral for cardiac surgery of patients who are currently considered to be unsuitable for revascularization, the referral of patients for revascularization who would at present be considered only for cardiac transplantation, and the avoidance of cardiac surgery in patients in whom revascularization would result in no functional benefit (but would carry significant risk of perioperative morbidity and mortality).

Both ^{201}Tl single-photon emission computed tomography (SPECT)[2-5] and low-dose dobutamine echocardiography (LDDE) have been proposed as effective techniques for the evaluation of myocardial viability.[6-11] Although LDDE is more widely available, it is unknown whether its efficacy and reliability equal those of ^{201}Tl SPECT, which is more established in this role.[2-5]

To determine the relative merits of the two imaging techniques, we compared ^{201}Tl SPECT and LDDE in the prediction of functional recovery in 38

patients with LV dysfunction who were undergoing coronary artery bypass graft surgery. Postoperative resting echocardiography at 3 months was used to determine LV improvement.

Methods

Study population

Forty-three patients with stable LV dysfunction who were to undergo coronary artery bypass graft surgery fulfilled the study inclusion criteria: ejection fraction of $\leq 40\%$ on contrast ventriculography, history of previous (>3 months old) myocardial infarction, one or more akinetic (Ak) or severely hypokinetic (SH) segments on preoperative resting echocardiography (16-segment left ventricular model), absence of recent episodes of unstable angina, absence of significant ($>50\%$) left main stem stenosis, and absence of (hemodynamically) significant valvular disease.

Five patients were withdrawn from the study because of perioperative myocardial infarction (3 patients), resection of all dyssynergic segments (1 patient), or inability to graft any of the Ak of SH segments (1 patient). Thirty-eight patients constituted the final study population. Mean patient age was 59 years (range, 36 to 73) and 26 were men. All patients were symptomatic - 36 had angina pectoris and 20 had dyspnea on effort. Mean angiographic LV ejection fraction was 31% (range, 18 to 40%). One-vessel disease, defined as diameter stenosis of a major coronary artery $>50\%$, was present in 3 patients; 16 patients had two-vessel disease; and 19 patients had three-vessel disease. Four patients had undergone previous coronary artery bypass graft surgery. Four patients were on ß-blockers during the preoperative diagnostic work-up.

Dobutamine stress echocardiography

The dobutamine stress test was performed as follows. A two-dimensional transthoracic echocardiogram in standard views and a 12-lead ECG were recorded with the patient at rest. Dobutamine was infused through an antecubital vein at doses of 5 and 10 $\mu g.kg^{-1}.min^{-1}$, for 3 minutes at each dose. Subsequently, three other steps from 20 to 40 $\mu g.kg^{-1}.min^{-1}$ (3 minutes each) were added. Finally, atropine (up to 1 mg) was injected when 85% of the maximal heart rate had not

been reached.[12] The echocardiogram was monitored during the test, and the last minute of each stage was recorded on videotape. The echocardiographic images were also digitized (on optical disk [Vingmed CFM 800] or on floppy disk [Esaote Biomedica SIM 7000]) and displayed side-by-side in quadscreen format to facilitate the comparison of images at rest and after dobutamine with subsequent postoperative images. A 3-lead ECG was monitored continuously, and a 12-lead ECG was recorded every minute. Blood pressure was measured by sphygmomanometer at each 3-minute stage.

Post-operative echocardiography

To assess the functional outcome of the dyssynergic segments, we obtained resting two-dimensional echocardiograms in all patients 3 months after cardiac surgery. In addition, high-dose dobutamine/atropine stress echocardiography was obtained in 32 patients.

Analysis of preoperative and postoperative echocardiograms

The interpretation of echocardiograms was performed by two experienced observers who were blinded to the clinical, angiographic and previous echocardiographic results of the individual patients. In a subset of 11 patients (176 segments), the interobserver and intraobserver variabilities of the classification of resting wall motion and the response to LDDE were also assessed. The assessment was based on both the digitized images displayed in a quadscreen format and a review of the images recorded on the videotape. The assessment was semiquantitative, and a 16-segment model[13] was used. The wall motion, including wall thickening, of every segment was scored with a 5-point scoring system, where 1 is normal wall motion and thickening, 2 is moderately hypokinetic, 3 is SH, 4 is Ak, and 5 is dyskinetic. We defined a segment as SH in the presence of minimal wall thickening with a limited inward motion of <2 mm; as Ak in the absence of systolic wall motion and thickening and, whenever possible, confirmed by M-mode tracing; and as dyskinetic in the presence of systolic outward wall motion with thinning.

Wall thickening was primarily used for the classification of wall motion, preventing the problem of postoperative paradoxical septal motion. Also, to reduce the confounding effect of tethering from adjacent segments, segmental wall

thickening was analyzed frame-by-frame during the first half of systole. Myocardial viability was judged to be present in a dyssynergic (either Ak or SH) segment when wall motion improved during the infusion of low-dose dobutamine by at least one point of the scoring system. Thus, a severe hypokinesis becoming moderately hypokinetic or systolic myocardial thickening becoming apparent in a previously Ak segment was considered a marker of viability. Myocardial ischemia was judged to be present when there was worsening by ≥ 1 of the segmental score. Ak and dyskinetic segments were not evaluated for this purpose.

Follow-up echocardiograms were compared with the corresponding preoperative resting images. For each segment, improvement of function was defined as a decrease of one or more grades. Moreover, we used the preoperative and postoperative wall motion score indexes (WMSIs) to evaluate the effect of revascularization on global LV function. WMSI was defined as the sum of the degrees of each segment divided by the total number of segments analyzed.

^{201}Thallium SPECT imaging

Briefly, as previously described,[14-16] ^{201}Tl (2 mCi) was injected intravenously 1 minute before the termination of the infusion of high-dose dobutamine (up to 40 $\mu g.kg^{-1}.min^{-1}$, with the addition of atropine if there were no signs of ischemia and if 85% of the maximal heart rate had not been reached). The acquisition of the poststress SPECT imaging was started within 10 minutes after the interruption of the dobutamine infusion. All images were acquired with a Siemens Gammasonics single-head Rota Camera (Orbiter) and a low-energy, all-purpose collimator. Thirty-two projections were obtained, from left posterior oblique to right anterior oblique, with an acquisition time of 45 seconds for each projection. A Gamma 11 computer system was used to process the tomographic data. Four hours after the stress imaging, a second acquisition was performed 20 minutes following the reinjection of 1 mCi of ^{201}Tl.

As previously described,[15,16] the interpretation of the images was based on six short-axis slices, three longitudinal slices, and three transverse long-axis slices (both stress and after reinjection). The analysis was performed visually with the assistance of quantitative measurement (circumferential profiles). The same 16-segment model used for interpretation of the echocardiograms was applied for the

interpretation of the SPECT images. Scintigraphic images from the short-axis and the long-axis views were matched with the echocardiographic images. Each defect was classified as fixed, partially reversible, or totally reversible. A myocardial segment was considered nonviable in the presence of a severe irreversible defect. A defect was classified as severe if the ^{201}Tl uptake of a segment was $<50\%$ of the uptake of the "normal" segments on the quantitative circumferential profile analysis and if it was consistent with a severe visually assessed defect. Scintigra phic definition of viability was based on the presence of normal ^{201}Tl uptake, totally reversible defect, partially reversible defect, or moderately severe fixed defect.

Statistical analysis

Continuous data are expressed as mean $\pm$ SD. Univariate analysis for categorical variables was performed using the chi-square test with Yate's correction. Differences were considered significant if the null hypothesis could be rejected at the .05 probability level. Sensitivity, specificity and positive and negative predictive values were based on their standard definitions and are reported with the corresponding 95% confidence interval (CI). The interobserver and intraobserver variabilities of regional wall motion pattern were assessed as percent agreement and *K* value.

Results

Pre-operative data

Of a total of 608 LV segments, 169 were classified as Ak and 51 as SH. Forty-three Ak segments were excluded from the postoperative evaluation because of aneurysmectomy (n = 41), or because they were not grafted (n = 2). Of the 51 SH segments, 7 were excluded from the postoperative evaluation because of aneurysmectomy (n = 3) or because they were not graftable (n = 4).

Low-dose dobutamine echocardiography

Only 14 of the 126 Ak segments that could be successfully revascularized showed the presence of wall thickening during low-dose dobutamine on preoperative echocardiogram. These 14 Ak segments were detected in 8 patients. Wall

Table 1 Relation among preoperative dobutamine echocardiographic results, viability on 201Tl single-photon emission computed tomography and postoperative outcome of wall motion in severely dyssynergic segments

LDDE pattern	No of segments	Thallium viability	Postoperative improvement
Ak -	112	49	9
Ak +	14	14	13
SH -	25	22	1
SH +	19	18	15

LDDE indicates low-dose dobutamine echocardiography, Ak: akinetic segments, SH: severely hypokinetic segments, and + or -: improvement or no improvement of wall motion during low-dose dobutamine infusion.

thickening improved during the infusion of dobutamine in 19 of the 44 SH segments. These 19 segments were present in 9 patients. Thus, viability was detected more frequently in SH than in Ak segments ($p < 0.0001$).

The interobserver and intraobserver concordances of resting wall motion analysis were 84% (K, 0.79) and 87% (K, 0.82), respectively. The interobserver and the intraobserver concordances of the response of wall motion during LDDE also were excellent: 92% (K, 0.84) and 94% (K, 0.86), respectively.

High-dose dobutamine echocardiography

At peak stress, new or worsening of preexisting wall motion abnormalities was detected in 163 of 576 segments (in 32 of the 36 patients). Angina occurred in 28 patients during the test.

^{201}Tl SPECT

^{201}Tl SPECT imaging indicated the presence of viable myocardium in 49 of 112 Ak regions not responding and in 14 of 14 Ak regions responding to dobutamine and in 22 of 25 SH regions not responding and in 18 of 19 SH regions responding to dobutamine (Table 1). From these data, it is clear that ^{201}Tl SPECT

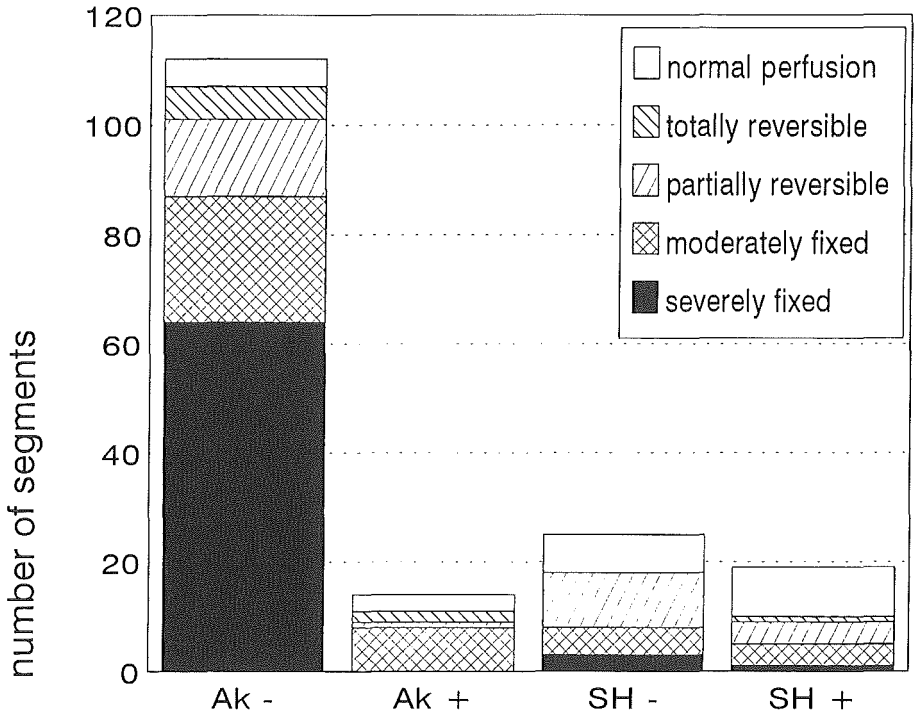

Figure Distribution of dobutamine/atropine-reinjection ^{201}Tl single-photon emission computed tomography perfusion patterns in four predefined low-dose dobutamine echocardiographic patterns.
Ak indicates akinetic segment, SH: severely hypokinetic segment, -: nonviable, +: viable, fixed: fixed perfusion defect, reversible: reversible perfusion defect.

indicates viable myocardium more frequently than LDDE ($p < 0.001$). The Figure displays the distribution of perfusion patterns by ^{201}Tl SPECT according to the different LDDE results.

Postoperative clinical and echocardiographic data

At 3 months after surgery, only 1 patient had angina and 10 patients still

complained of dyspnea on effort.

Improvement of regional wall motion

Resting echocardiograms at 3-months postoperative follow-up revealed an improvement of wall motion in 38 (22%) of the 170 dyssynergic segments. The improvement was found in 22 (17%) of the 126 Ak segments (change to SH in 6 segments, to moderate hypokinesis in 13 segments and to normal in 3 segments) and in 16 (36%) of the 44 SH segments (change to moderate hypokinesis in 8 segments and to normal in 8 segments) ($p = .02$).

Reduction of dobutamine induced myocardial ischemia

Of 32 patients who underwent a high-dose dobutamine stress test during follow-up, 3 had angina at peak stress. New or worsened wall motion abnormalities were detected in 10 patients and in 23 of 512 LV segments.

Prediction of regional improvement

Postoperative improvement occurred in 28 of the 33 segments that improved during LDDE and in only 10 of 137 segments that did not improve (Table 1). Of the segments judged to be viable by LDDE, postoperative improvement occurred in 79% of SH segments and in 93% of Ak segments.

^{201}Tl SPECT detected the presence of viable myocardium in 32 of the 33 matched segments considered viable by LDDE. Despite the frequent indication of viability by ^{201}Tl SPECT in the Ak segments unresponsive to dobutamine (44%), improvement after surgery was found in only 8% of these segments. Similarly, wall thickening improved after revascularization in only 1 of the 25 SH regions unresponsive to dobutamine, despite signs of viability by ^{201}Tl SPECT in 22 of these 25 segments. Table 2 shows the predictive accury with 95% CI of the two methods for the postoperative improvement of SH and of AK segments.

Global left ventricular function

The WMSI revealed that there were no significant differences before and after coronary artery bypass graft surgery in either the subset in whom myocardial viability was predicted by LDDE (13 patients) (2.6 ± 0.5 versus 2.4 ± 0.4) or in

Table 2 Diagnostic accuracy with 95% confidence intervals of low-dose dobutamine echocardiography and high-dose dobutamine-reinjection ^{201}Tl SPECT for prediction of postoperative improvement of wall motion in severely dyssynergic segments

Method	Sensitivity	Specificity	PPV	NPV
LDDE, %	74	96	85	93
95% CI	67 to 81	93 to 99	80 to 90	89 to 97
Tl SPECT, %	89	48	33	94
95% CI	84 to 94	40 to 56	26 to 40	90 to 98

PPV indicates positive predictive value, NPV: negative predictive value, LDDE: low-dose dobutamine echocardiography, SPECT: single-photon emission computed tomography, CI: confidence interval.

the entire study population (2.3 $\pm$ 0.5 versus 2.3 $\pm$ 0.5).

Coronary angiography

A routine coronary angiogram independent of the recurrence of symtoms was undertaken in 14 patients at 3-month follow-up. Sustained patency of the grafts to the Ak or SH segments was demonstrated in all of these patients.

Discussion

The functional assessment of hibernating myocardium and the presence of viability is clinically challenging[3] and of paramount importance for the selection of the most appropriate individual treatment for patients with chronic severe LV dysfunction.[1]

We prospectively studied a group of patients with severe chronic LV dysfunction who were candidates for surgical revascularization (1) to assess the prevalence of regional improvement of Ak and SH segments after surgical revascularization and (2) to evaluate the roles of LDDE and ^{201}Tl SPECT for predicting such improvement. In addition, the reversibility of stress-induced myocardial ischemia was assessed by clinical judgement and high-dose dobutamine

stress test.

In this series of patients, improvement of regional function after revascularization was found in 22% of Ak and SH segments. This percentage is lower than that of other series[7,9,10] and might be related to the selection of patients with severely impaired LV function in a tertiary referral center with an ongoing heart transplantation program.

We have demonstrated that preoperative LDDE is both a sensitive (28 of 38 segments) and a specific (127 of 132 segments) predictor of postoperative outcome of regional myocardial function. The pattern of improvement of wall thickening in severely dyssynergic regions during the infusion of low-dose dobutamine was found to be a reliable predictor of functional recovery of wall motion after successful and uncomplicated surgical revascularization, with a positive predictive value of 85% (95% CI, 80% to 90%), whereas the pattern of Ak or SH unresponsive to low-dose dobutamine is indicative of nonviable tissue and offers a negative predictive value of 93% (95% CI, 89% to 97%).

^{201}Tl SPECT (matched for echocardiographic segments) indicated the presence of viable myocardium more frequently than LDDE (103 of 170 versus 33 of 170). However, this imaging technique appears to be less suitable than LDDE to predict the postoperative improvement of regional wall motion in patients with severe LV dysfunction. In particular, the high prevalence of viability detected before surgery by ^{201}Tl SPECT and the low prevalence of postoperative functional improvement result in a low specificity and in a low positive predictive value (Table 2).

Overestimation of myocardial viability by perfusion scintigraphy may relate to several factors. First, scintigraphy may detect islands of jeopardized vital myocardial cells of inadequate size to revert LV dysfunction despite successful revascularization. Second, tethering by scar tissue may restrict the improvement in wall motion of adjacent viable segments. Third, functional recovery may not be complete by 3 months ("embalmed myocardium").[17] Finally, since subendocardial layers play a major role in wall motion, a necrosis limited to the subendocardium may result in severe dyssynergy despite the presence of viable myocardium in the subepicardial layers.[18]

In our study group, there was no significant postoperative improvement of

global LV function; however, bypass surgery alleviated myocardial ischemia, since the number of patients with angina and the extent of stress induced ischemia were greatly reduced. This is consistent with the high postoperative patency rate of bypass coronary grafts and confirmed the usefulness of dobutamine stress echocardiography in the assessment of stress-induced myocardial ischemia after coronary revascularization.[12]

Previous studies

Although several studies[6-8,11,19] have addressed the role of dobutamine echocardiography for the assessment of LV functional recovery in patients with recent myocardial infarction, few data are available regarding its predictive value for postrevascularization functional improvement.[9,10] In two previous studies on postrevascularization recovery, Marzullo et al[9] and Cigarroa et al[10] reported a higher incidence of wall thickening during low-dose dobutamine in Ak regions (47% and 39%, respectively, compared with 11% in the present study). This discrepancy may relate to different methodologies (absence of subclassification for SH segments in their studies) and patient selection (inclusion in the present study of patients with more severe and more longstanding ventricular dysfunction, where stunned myocardium is less likely to be present). Considering the value of LDDE in predicting postoperative functional outcome, our findings are in agreement with those of the two previous reports.

Study limitations

First, the number of viable Ak and SH segments identified in the present study was limited despite our analysis of 608 segments both before and after coronary bypass graft surgery. This, however, reflects our stringent inclusion criteria and our strict method of analysis (panel review with simultaneous, quad-screen format).

Second, we arbitrarely timed the outcome of dyssynergic segments 3 months after surgical revascularization. However, it cannot be excluded that functional improvement can also occur later.

Finally, we focused on the postoperative phase of regional wall motion. We are aware that the improvement in a limited area of myocardium can be clinically not

relevant to global LV function. However, this was not the primary aim of the study.

Conclusions

Our observations in the setting of severe chronic LV dysfunction indicate that 1) wall thickening during low-dose dobutamine in Ak segments is infrequent, 2) responsiveness of Ak and SH segments to low-dose dobutamine is both a specific and a sensitive predictor of postrevascularization functional improvement, and 3) compared with LDDE, ^{201}Tl SPECT has an equivalent sensitivity for the prediction of postoperative myocardial functional improvement but a lower specificity. Thus, LDDE should be the preferred imaging technique for predicting the functional outcome of patients with severe LV dysfunction who are under consideration for coronary artery bypass graft surgery.

Acknowledgements

We are deeply grateful to Eric Boersma, MSc for the statistical assistance. Also, we appreciate the co-operation of the referring Rijnmond cardiologists.

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Addendum

Correspondence

Prediction of improvement of regional left ventricular function after surgical revascularization.

Circulation 1996;93:396-397

To the editor:

Arnese et al[1] in the article titled: "Prediction of improvement of regional left ventricular function after surgical revascularization" concluded that compared with low-dose dobutamine echocardiography (LDDE), ^{201}Thallium single photon emission computed tomography (SPECT) imaging has an equivalent sensitivity for the prediction of postoperative myocardial functional improvement but a lower specificity. Thus, LDDE should be the preferred imaging technique for predicting the functional outcome of patients with severe left ventricular dysfunction who are under consideration for coronary artery bypass surgery. In this article, the specificity and positive predictive value of dobutamine ^{201}Thallium imaging with reinjection were significantly lower (48% and 33%, respectively) compared with LDDE.

The lower specificity and positive predictive value compared with other studies[2-4] may be attributable to the fact that moderate fixed defects on ^{201}Thallium imaging were considered viable.

As shown in the Figure, the largest percentage of "false-positive" ^{201}Thallium results were noted in the segments with moderate fixed defects.

Although it is true that viabilitiy has been shown in fixed defects of mild or moderate severity using positron emission tomography imaging with ^{18}FDG[4], resting wall motion may not improve post-revascularization in these segments if they are composed of an admixture of scar tissue and viable tissue (normally perfused at rest). However, other benefits such as symptomatic improvement and reduction of ventricular remodeling may be derived from revascularizing these segments. The specificity and positive predictive value of viability assessment by

SPECT ^{201}Thallium imaging may be significantly better if other clinical outcomes are considered.

The authors demonstrate a difference in the ability to predict the functional outcome of *myocardial segments* between dobutamine echocardiography and ^{201}Thallium imaging. Consequently, it is inappropriate to conclude that LDDE should be the preferred imging technique for predicting the functional outcome of *patients* with severe left ventricular dysfunction who are under consideration for coronary artery bypass surgery.

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Response:

We appreciate the interest of Dr Akinboboye in our work. In response to his comments, we want to recall the aim of our study.[1] This study was undertaken to compare ^{201}Tl stress-reinjection single photon emission computed tomography with

low-dose dobutamine echocardiography (LDDE) in the prediction of improvement of regional left ventricular function after surgical revascularization. The study group comprised mostly patients with severe regional and global chronic left ventricular dysfunction. To our knowledge only three other studies,[2-4] including Ohtani et al[3] but not Bonow et al,[5] have used ^{201}Tl stress-reinjection protocols for the prediction of improvement of regional left ventricular dysfunction after revascularization. In these, a limited number of patients (n = 55) was studied and the majority of patients had well or relatively well preserved left ventricular function. A highly variable specifity from 40%[4] to 80%[2] has been reported, and in the largest series of patients, studied by Ohtani et al,[3] 25% of the preoperatively hypoperfused segments had normal wall motion but were still included in the analysis. Furthermore, in these studies no distinction was made between moderately and severely fixed perfusion defects, possibly explaining the variability of the specificity of the test.

Indeed as shown in the Figure in our article, the reported specificity and positive predictive value may be influenced by the fact that moderately fixed perfusion defects, although in comparative "state-of- the-art" studies with FDG positive emission tomography (PET) mostly viable, were considered viable. For predicting reversibility of wall motion abnormalities this may not be the case. Therefore, we re-analyzed our data with the assumption of nonviability of moderately fixed defects. Of the 40 moderately fixed defects, 13 recovered postoperatively, resulting in an increase in specificity from 48% to 68% but with a much lower sensitivity of 55%.

It is highly speculative to suggest that revascularization of moderately fixed defects may lead to symptomatic improvement or reduction of ventricular remodeling. There are no studies to support this hypothesis. On the contrary, PET data show that only patients with jeopardized myocardium (mismatch pattern) benefit from revascularisation, in terms of symptomatic improvement or prognosis.[6]

About the last comment, we agree that our statement in the conclusions ("low dose dobutamine echocardiography should be the preferred imaging technique for predicting the functional outcome of *patients*") is inappropriate based on the reported results. However, preliminary results from our institution suggest

that an improvement of global left ventricular function is highly likely to occur when at least 25% of the myocardium is akinetic and is responsive to dobutamine.[7]

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Chapter 8

^{18}F-Fluorodeoxyglucose SPECT for the Prediction of Reversibility of Ventricular Dysfunction After Revascularization

A Comparison with Rest-Redistribution ^{201}Thallium SPECT

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Submitted for publication

Abstract

Background

Improvement of left ventricular dysfunction after coronary revascularization can be predicted by positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG) as a metabolic marker. We evaluated the use of FDG in combination with single photon emission computed tomography (SPECT) and compared this technique with rest-redistribution ^{201}Thallium (^{201}Tl) SPECT to predict functional recovery after revascularization.

Methods

Fifty-five patients with regional wall motion abnormalities were studied with FDG SPECT during hyperinsulinemic glucose clamping. Subsequently a resting ^{201}Tl SPECT was performed to assess myocardial perfusion, 24 patients also underwent redistribution ^{201}Tl SPECT. Regional contractile function was evaluated with echocardiography, using a 13-segment model and a 4-grade scoring system, before and 3 months after revascularization. Left ventricular ejection fraction (LVEF) was also determined, either by echo (n = 37) or by radionuclide ventriculography (n = 18). The SPECT data were analyzed quantitatively and the optimal diagnostic accuracy for functional recovery was determined using receiver-operating characteristic analysis.

Results

One third of dysfunctional segments showed improvement of wall thickening at follow-up. The FDG approach reached a sensitivity of 85% (95% confidence interval [CI], 78% to 92%) and a specificity of 75% (95% CI, 69% to 81%) to predict regional functional recovery. Similar results were obtained in the subgroup of patients with a LVEF of $\leq$30% (n = 22). LVEF improved from 28 $\pm$ 8% to 35 $\pm$ 9% ($p < 0.05$) in patients with $\geq$3 viable segments on FDG SPECT. In patients with $\leq$2 viable segments LVEF remained unchanged. In direct comparison FDG SPECT showed a better specificity (77% (95% CI, 67% to 87%) versus 57% (95% CI, 45% to 69%)) as compared to rest-redistribution ^{201}Tl SPECT. Stepwise logistic regression analysis of the FDG and ^{201}Tl rest-redistribution data showed that increased FDG uptake in perfusion defects was the best predictor of

functional recovery. All other parameters did not contribute independently.

Conclusions

This study shows that FDG SPECT is superior to rest-redistribution ^{201}Tl SPECT in the identification of patients in whom regional and global LV function can improve after revascularization. The SPECT approach may contribute to a more routine use of FDG for management of patients with chronic ischemic LV dysfunction.

Introduction

Heart failure is an increasing problem in cardiology due to its rising incidence over the last decade. In coronary artery disease impaired left ventricular (LV) function is not necessarily an irreversible process as recovery of LV function after revascularization has been demonstrated. The concepts of hibernation and repetitive stunning have been introduced to explain such improvement.[1,2] Nesto et al have described improvement in left ventricular ejection fraction (LVEF) and favourable prognosis after revascularization of viable myocardium.[3] Thus, the differentiation between viable and scarred myocardium may have important clinical implications.

Identification of viable myocardium is possible with positron emission tomography (PET) using [^{18}F]fluorodeoxyglucose (FDG).[4,5] Reversibility of regional wall motion abnormalities after revascularization has been demonstrated in regions with normal perfusion and in hypoperfused regions with relatively preserved FDG uptake (FDG-perfusion mismatch). In contrast, regions with hypoperfusion and concomitantly decreased FDG uptake (FDG-perfusion match) did not show recovery of function.[6-12] Improvement of global LV function has also been observed in patients with viable myocardium on FDG PET.[6,11,12]

Relatively few PET devices are avialable for clinical use. Therefore, several laboratories have evaluated the feasibility of imaging myocardial FDG uptake with SPECT using 511 keV collimators.[13-18] No data however are available on the diagnostic value of FDG SPECT to predict functional recovery after revascularization. Therefore, the aim of the present study was to evaluate whether FDG SPECT can predict improvement of resting wall motion abnormalities after

revascularization. For comparison of regional FDG uptake with regional perfusion early resting ^{201}Tl SPECT was performed.[19] In addition the results were compared with rest-redistribution ^{201}Tl SPECT, which is currently one of the most widely used techniques to assess myocardial viability.[20-24]

Methods

Study population

We prospectively studied 55 consecutive patients referred for coronary revascularization: all had chronic regional wall motion abnormalities at rest observed on LV angiography and on two-dimensional echocardiography. Forty-five patients (82%) underwent coronary artery bypass graft surgery (CABG), 10 patients (18%) a percutaneous transluminal coronary angioplasty (PTCA). The time-interval of the SPECT study to revascularization was 2.0 $\pm$ 2.7 months. The SPECT studies were performed in patients who were already scheduled for revascularization. The results did not influence patient management.

Study protocol

All patients underwent an early resting ^{201}Tl SPECT, followed by FDG SPECT during a hyperinsulinemic euglycemic clamp. In 24 of these patients rest-redistribution ^{201}Tl SPECT was performed. Improvement of regional wall motion was determined from serial resting echocardiograms before and 3.4 $\pm$ 2.5 months after revascularization. To assess improvement of LVEF 18 patients had radionuclide ventriculography before and after revascularization, whereas in the remaining 37 patients LVEF was calculated from echocardiograms. The SPECT studies were performed preferably on the same day, with a maximum interval of 1 week. Medication was continued during the study. Each patient gave informed consent to the study protocol that was approved by the ethical committees of the participating hospitals.

^{201}Tl SPECT

To delineate regional myocardial perfusion a resting ^{201}Tl SPECT was performed as described previously.[18,19] After an overnight fast, a single dose of 111 MBq (3 mCi) ^{201}Tl chloride was administered intravenously at rest. Imaging was

started 10 to 15 minutes after injection. In 24 patients a redistribution image was acquired, 4 hours after tracer injection. A large-field-of-view rotating dual head gamma camera (ADAC Laboratories, Milpitas CA) was used, equipped with a low-energy high-resolution (LEHR) collimator. The energy was centered on the 89 keV photon peak with a 20% window and on the 167 keV photon peak with a 20% window. The dual head gamma camera system was rotated over 360°, collecting 64 views for 30 seconds each, resulting in a total data collection time of 16 minutes. Data were stored in a 64 x 64, 16-bit matrix. From the raw scintigraphic data 6 mm-thick (1 pixel) transaxial slices were reconstructed by filtered back projection using a Hanning filter (f_c = 0.63 cycle/cm). Slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis projections perpendicular to the heart-axis.

FDG SPECT

FDG (t½ of ^{18}F = 110 min) was produced and synthesized at the cyclotron facility of the Free University Amsterdam according to previously described methods.[25] The radiochemical purity of the product was 98%. After an overnight fast, subjects underwent a hyperinsulinemic glucose clamp[26] to standardize metabolic conditions throughout FDG SPECT. FDG (185 MBq, 5 mCi) was injected after 60 min of clamping, another 45 min was allowed for myocardial FDG uptake.[27,28] Data acquisition was performed with the same camera system as described for ^{201}Tl. Especially designed collimators were used for the detection of 511 keV photons (van Mullekom, Nuclear Fields, Boxmeer, The Netherlands).[29] Reconstruction of data was identical to that of ^{201}Tl SPECT.

Hyperinsulinemic euglycemic clamping

For this purpose, 2 catheters were placed in the left and right antecubital veins. One catheter was used for separate infusions of glucose and insulin. The contralateral catheter was used for the administration of FDG and to draw plasma samples to monitor glucose levels. Insulin (Human Velosulin, Novo Nordisk, 100 IE/ml) in 0.65% sodium chloride was used. To prevent adhesion of insulin to the infusion system 3.8 ml human albumin (20% Human Albumin, CLB) was added. The insulin infusion rate was 100 mU/kg/hr and was not changed throughout

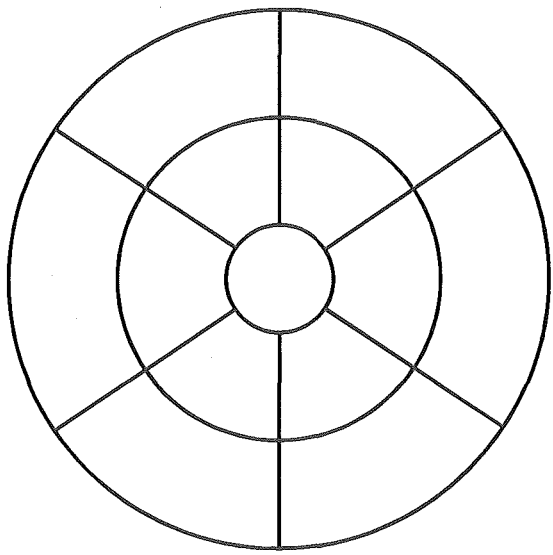

Figure 1 The left ventricular myocardium is divided into 13 regions. The basal regions are at the periphery and the apex is located in the center of the polar map.

clamping to achieve a hyperinsulinemic state. Glucose infusion (500 ml 20% glucose with 20 ml 14.9% potassium chloride to prevent hypokalemia) was started at a rate of 6 mg/kg/min and was adjusted every 10 min to maintain normoglycemia.

Image analysis

Circumferential count profiles (60 radii, highest pixel activity/radius) from FDG and ^{201}Tl short-axis slices were generated. To obtain uniformity in the number of slices, twenty slices were acquired by linear interpolation of the available slices and presented as a polar map. Each polar map was adjusted to peak myocardial activity (100%). The inner 4 slices were assigned to the apex, the middle 8 slices to the distal myocardium and the outer 8 slices to the basal myocardium. The polar maps were divided into 13 segments as demonstrated in Figure

1. A region of normal perfusion was drawn on the early ^{201}Tl polar map. This region was defined as the area with the highest ^{201}Tl uptake associated with normal wall motion on the echocardiogram. The activity of this area was normalized to the mean activity of the same area of a data base containing data of normal individuals[14]. All other polar map data were adjusted subsequently. The region of normal perfusion was projected on the FDG polar map and the same normalization procedure was followed. For this purpose another database containing data on FDG activities in normal individuals was used.[14] Pixels with a ^{201}Tl activity <2 SD below the normal reference value were considered abnormal. The extent of the perfusion defects within each of the 13 segments was expressed as the percentage of abnormal pixels relative to the total number of pixels/segment. A perfusion defect was considered present only if the extent exceeded 15% of the myocardial segment. The ^{201}Tl and FDG activities were expressed as percentage of the corresponding normal reference values.

Definition of myocardial viability

For the FDG SPECT approach a segment was considered viable if perfusion was normal or if FDG uptake was relatively increased in a perfusion defect.[4,5] The cut-off level of increased FDG uptake was defined by receiver-operating characteristic (ROC) analysis.

For the rest-redistribution ^{201}Tl SPECT approach a segment was considered viable if perfusion was normal, if significant redistribution occurred in a perfusion defect or if segmental ^{201}Tl activity on the late image exceeded a threshold.[20-24] The optimal cut-off levels for ^{201}Tl redistribution and ^{201}Tl activity were defined by ROC analysis.

Assessment of improvement of regional dyssynergy

Regional wall motion was assessed by resting echocardiography before and after revascularization. Echocardiographic images were recorded on videotape. Four standard views of the left ventricle were obtained: parasternal long- and short-axis views and apical two- and four-chamber views. The images were reviewed off-line and consensus was achieved by 2 observers unaware of the SPECT data. For comparison with the SPECT data the left ventricle was divided

into 13 comparable segments.[30] Both inward wall motion and wall thickening were analyzed. Each segment was assigned a wall motion score (WMS) of 0 to 3: normal = 0, hypokinetic = 1 (decreased endocardial excursion and systolic wall thickening), akinetic = 2 (absence of endocardial excursion and systolic wall thickening), and dyskinetic = 3 (paradoxic outward movement in systole). The pre- and post-interventional images were compared on a segmental basis. Post-interventional improvement of regional wall motion was considered if systolic thickening (hypo- or normokinesia) was detected in a prior a- or dyskinetic segment, or if normal wall motion was detected in hypokinetic segments. Only segments that were succesfully revascularized were analyzed. Wall thickening was primarily utilized for the classification of septal wall motion, thereby preventing the problem of paradoxical septal motion after CABG.[31] We previously reported a low level of inter- and intra-observer variability for the classification of resting wall motion (agreement 84% and 87%).[32]

Assessment of improvement of global ventricular function

Serial LVEF measurements were obtained using radionuclide ventriculography in 18 patients. This was performed at rest with the patient in supine position after intravenous administration of 740 MBq of ^{99m}technetium. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp, Iselin, NJ, USA), oriented in the 45° left anterior oblique position with a 5-10° caudal tilt. LVEF was calculated from the 45° left anterior oblique view by an automated technique. In 37 patients LVEF was calculated by cross-sectional echocardiography utilizing the apical biplanar Simpson's technique.[33]

Improvement of global function after revascularization was defined as an increase of LVEF $\geq 5\%$, exceeding our reproducibility limits.

Statistical analysis

All results were expressed as mean $\pm$ SD. Patient data were compared using the Student's *t*-test for paired and unpaired data when appropriate. Comparison of proportions was performed using chi-square analysis. A *p*-value of <0.05 was considered significant. ROC analysis was performed to determine the optimal cut-off point for increased FDG uptake, ^{201}Tl redistribution and ^{201}Tl activity for the

prediction of functional recovery.

The best cut-off point of increased FDG uptake and ^{201}Tl redistribution had to exceed our reproducibility limits (>4%). The optimal cut-off was chosen as the maximal sum of sensitivity and specificity. Sensitivity, specificity, positive and negative predictive values rely on the standard definition and are reported with 95% confidence intervals (CI). Stepwise logistic regression analysis was performed to determine which parameters (such as early and late ^{201}Tl activities, ^{201}Tl redistribution, FDG activity, increased FDG uptake in perfusion defects, extent of perfusion defect, severity of resting wall motion abnormalities before revascularization) independently predict absence or presence of functional recovery.

Results

Patient characteristics

The clinical characteristics of the study population are presented in Table 1. Fifty-one patients (93%) had a previous infarction. The time-interval of infarction to the SPECT study was more than 1 month in 93% of the patients. Eight patients had diabetes mellitus type II, which was well-regulated on oral medication. All patients had significant coronary artery disease on angiography. They had a mean LVEF of 39%; 22 patients had an LVEF $\leq$30%.

Baseline characteristics

Of a total of 715 segments analyzed by echocardiography, 305 (43%) showed abnormal wall motion. The mean number of abnormal segments per patient was 5.5 $\pm$ 3.1. Twenty-four segments were excluded from analysis due to inadequate revascularization. Therefore, 281 dyssynergic segments were selected for serial analysis. Hypokinesis was observed in 128 segments (46%), whereas 153 were akinetic/dyskinetic (54%). Forty-nine segments (17%) showed normal perfusion on ^{201}Tl SPECT.

Prediction of regional functional recovery by FDG SPECT

Using recovery of wall motion abnormalities as "golden standard", 281 segments with abnormal wall motion at baseline were divided into 2 groups: segments with improvement after revascularization (group I, n = 94) and segments

Table 1 Clinical characteristics of the study population

	FDG SPECT n = 55	FDG / RR SPECT n = 24
Sex (M/F)	49 / 6	21 / 3
Age (yr) (mean ± SD)	62 ± 10	65 ± 8
Previous infarction (%)	51 (93)	18 (86)
Q wave (%)	36 (71)	14 (78)
Anterior	18	6
Inferior	18	8
AP NYHA class (mean ± SD)	2.2 ± 0.8	2.2 ± 0.9
coronary arteriography	55	24
3 vessel disease (%)	37 (67)	12 (50)
2 vessel disease (%)	11 (20)	9 (38)
1 vessel disease (%)	7 (13)	3 (12)
LVEF (%) (mean ± SD)	39 ± 14	45 ± 15
Previous CABG (%)	11 (20)	5 (24)
Previous PTCA (%)	4 (7)	0 (0)

AP: angina pectoris, CABG: coronary artery bypass grafting, FDG: [^{18}F]-fluoro-deoxyglucose, LVEF: left ventricular ejection fraction, PTCA: percutaneous transluminal coronary angioplasty, RR ^{201}Tl: rest redistribution thallium.

without improvement (group II, n = 187). The differences in echocardiographic and scintigraphic characteristics between the 2 groups are presented in Table 2. In group I segmental WMS decreased from 1.6 ± 0.5 to 0.5 ± 0.5. The extent and the ^{201}Tl activity of the perfusion defects were comparable in group I and II. In group I FDG uptake was increased as compared to ^{201}Tl uptake ($p < 0.0001$). In contrast FDG and ^{201}Tl activities were comparable in group II (p = NS). An example of ^{201}Tl and FDG polar maps of a patient with increased FDG uptake is

Table 2 Comparison between characteristics of segments with improvement in segmental WMS (group I) and segments without improvement (group II) after revascularization

	Group I (n = 94)	Group II (n = 187)	*p*-value
segmental WMS pre	1.6 ± 0.5	1.6 ± 0.6	NS
segmental WMS post	0.5 ± 0.5	1.6 ± 0.6	< 0.001
No of segments without perfusion defect (%)	28 (30)	21 (11)	< 0.01
Extent of ^{201}Tl defect (%)	76.3 ± 27.8	77.7 ± 24.1	NS
^{201}Tl activity (%)	71.3 ± 8.6	70.4 ± 11.2	NS
FDG activity (%)	84.4 ± 13.0	70.5 ± 13.3	< 0.0001
FDG - ^{201}Tl activity (%)	13.1 ± 13.5	0.1 ± 9.1	< 0.0001

FDG: F18-fluorodeoxyglucose, ^{201}Tl: thallium-201, WMS: wall motion score.

presented in Figure 2.

ROC analysis revealed a 7% difference between FDG and ^{201}Tl activity as the optimal cut-off to discriminate segments that improve or do not improve (sensitivity 79%; specificity 85%) (Figure 3). Applying the definition of myocardial viability, FDG SPECT showed a sensitivity of 85% (CI 78% to 92%) and a specificity of 75% (CI 69% to 81%), with a positive predictive value of 63% (CI 55% to 71%) and a negative predictive value of 91% (CI 86% to 96%).

Stepwise logistic regression showed that increased FDG uptake in perfusion defects was the best predictor of recovery of function. After its withdrawal all other parameters did not contribute significantly. Sensitivity and specificity for the prediction of functional recovery were also determined in different subgroups according to severity of dyssynergy, localization of dyssynergy and LVEF (Table 3). In hypokinetic segments specificity was significantly lower in comparison to akinetic/dyskinetic segments (66% (CI 56% to 76%) versus 84% (CI 77% to 91%)). In inferior and septal regions the diagnostic accuracy was similar in comparison to apical, anterior and lateral regions.

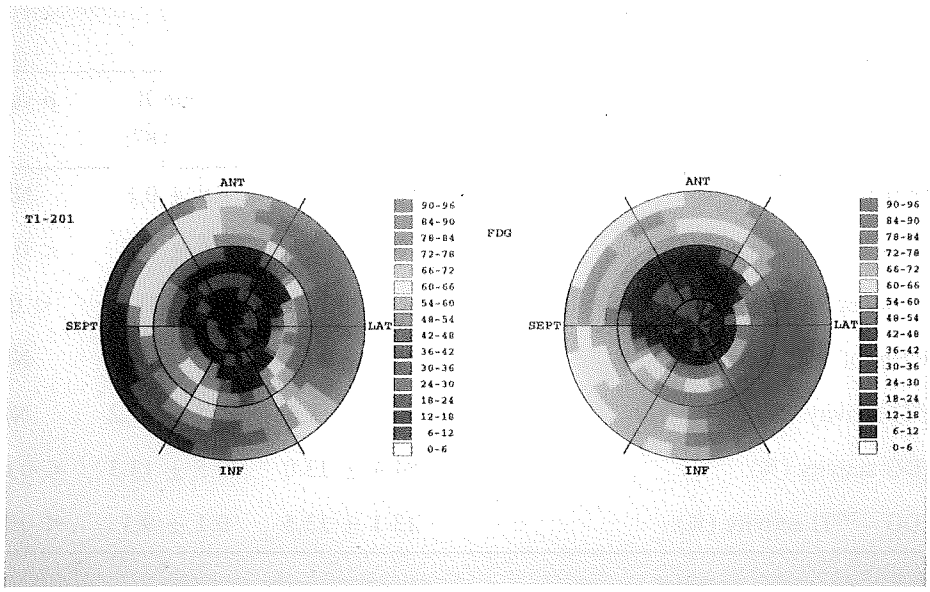

Figure 2 Normalized polar map displays for ^{201}Tl and FDG in a patient with perfusion defects in the apex and the basal inferior and septal regions. All regions showed increased FDG uptake.

In patients with a LVEF $\leq$30% FDG SPECT showed a sensitivity and specificity of 89% (CI 80% to 98%) and 72% (CI 64% to 80%).

Prediction of recovery of global LV function by FDG SPECT

Patients were classified into 2 groups: group A consisted of 19 patients with 3 or more viable dyssynergic segments on FDG SPECT and group B consisted of 36 patients with 2 or less viable dyssynergic segments. LVEF increased significantly in group A from 28 $\pm$ 8% before to 35 $\pm$ 9% (p <0.05) after revascularization. In group B LVEF remained unchanged (45 $\pm$ 14% versus 44 $\pm$ 14%, p = NS).

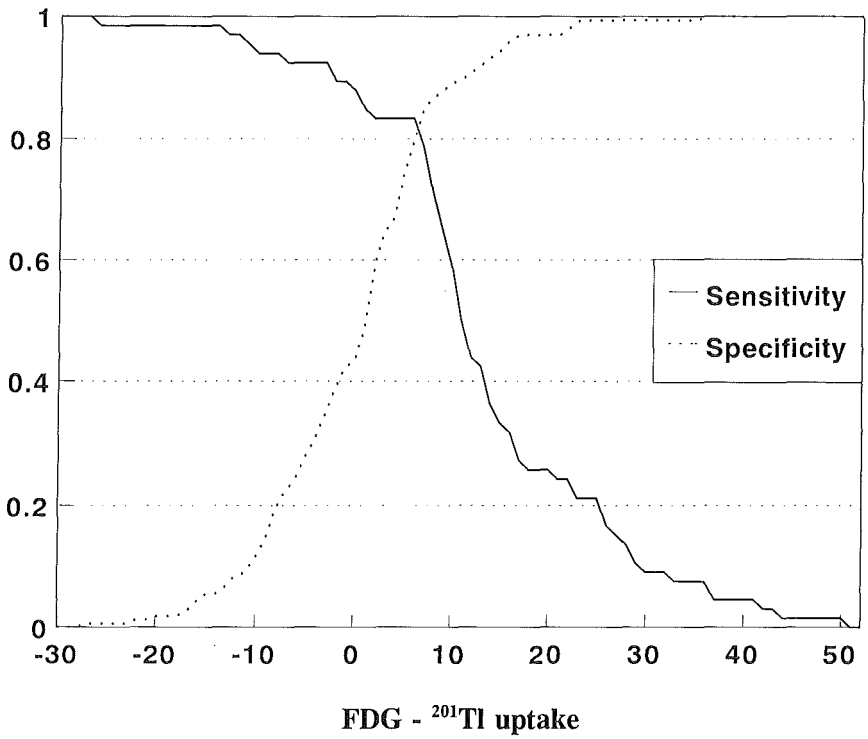

Figure 3 Percentage correct classification of presence (sensivity) or absence (specificity) of contractile improvement of dyssynergic segments after revascularization as a function of cut-off points over the whole spectrum of FDG - ^{201}Tl activity. At a cut-off level of 7% increased FDG uptake the optimal sum of sensitivity (79%) and specificity (85%) was reached.

We also analyzed the 22 patients with a LVEF $\leq$30%, since improvement of LVEF in these patients is of utmost clinical relevance (Figure 4).
In 14 patients with 3 or more viable segments LVEF improved significantly from 25 $\pm$ 6% to 32 $\pm$ 6% ($p < 0.05$). LVEF remained unchanged in 8 patients with 2 or less viable segments (24 $\pm$ 6% versus 25 $\pm$ 6%, p = NS).

Considering an increase of LVEF of $\geq$5% as improvement on a patient basis, FDG SPECT correctly identified 12/12 (100%) of the improvers as viable, whereas 8/10 (80%) of the non-improvers were identified as nonviable.

Table 3 Sensitivity and specificity of FDG SPECT with 95% confidence intervals for prediction of functional recovery after revascularization in different subsets of segments

	sensitivity % (CI)	specificity % (CI)
Total number of segments (n = 281)	85 (78-92)	75 (69-81)
Hypokinetic segments (n = 128)	82 (72-92)	66 (56-76)
A-/Dyskinetic segments (n = 153)	87 (78-96)	84 (77-91)
Ant/Apic/Lat segments (n = 139)	86 (76-96)	76 (67-85)
Inf/Sept segments (n = 142)	84 (73-95)	75 (66-84)
Segments of pts with LVEF >30% (n = 109)	80 (68-92)	81 (72-90)
Segments of pts with LVEF ≤30% (n = 172)	89 (80-98)	72 (64-80)

Ant: anterior, Apic: apical, CI: 95% confidence intervals, Inf: inferior, Lat: lateral, LVEF: left ventricular ejection fraction, Pts: patients, Sept: septal.

Comparison between FDG and rest-redistribution ^{201}Tl SPECT

In the subgroup of 24 patients 106 adequately revascularized dyssynergic segments were analyzed. Thirty-six segments (34%) improved in regional wall motion and 70 (66%) showed no improvement. Segments which improved had significantly higher ^{201}Tl activity at late acquisitions (81.7 ± 15.5% versus 74.7 ± 13.4%, $p < 0.05$) and more redistribution (5.1% ± 7.5% versus 0.4 ± 5.1%, $p < 0.01$) as compared to those segments which did not improve.

Based on ROC analysis the optimal cut-off point for the difference between rest (early) and redistribution (late) ^{201}Tl activity was 5%, whereas the optimal cut-off point for ^{201}Tl activity on the second ^{201}Tl acquisition was 75%. Using the 5% redistribution criterium for viability, rest-redistribution ^{201}Tl SPECT showed a sensitivity of 69% and a specificity of 73% (Figure 5).

After exclusion of dyssynergic segments with normal perfusion, sensitivity and specificity were 58% and 84% respectively. Figure 5 also shows the results when applying the 75% activity level for viability and when combining both criteria.

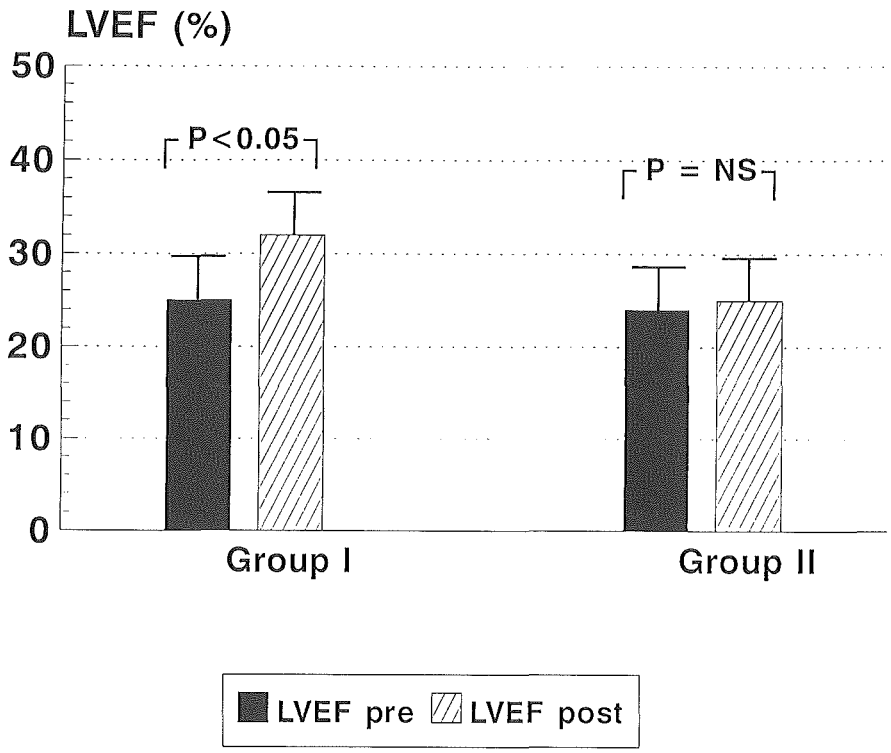

Figure 4 Bar graph illustrating LVEF before and after revascularization in patients with a LVEF ≤30%. In patients (group I) with 3 or more viable segments on FDG SPECT LVEF increased from 25 ± 6% to 32 ± 6%. In patients (group II) with 2 or less viable segments LVEF remained unchanged (24 ± 6% versus 25 ± 6%).

Rest-redistribution ^{201}Tl SPECT consistently revealed a lower diagnostic accuracy compared to the FDG SPECT approach in the same group of patients.

Stepwise logistic regression analysis of FDG and rest-redistribution ^{201}Tl data showed that increased FDG uptake in perfusion defects was the best predictor of functional recovery. All other parameters did not contribute independently.

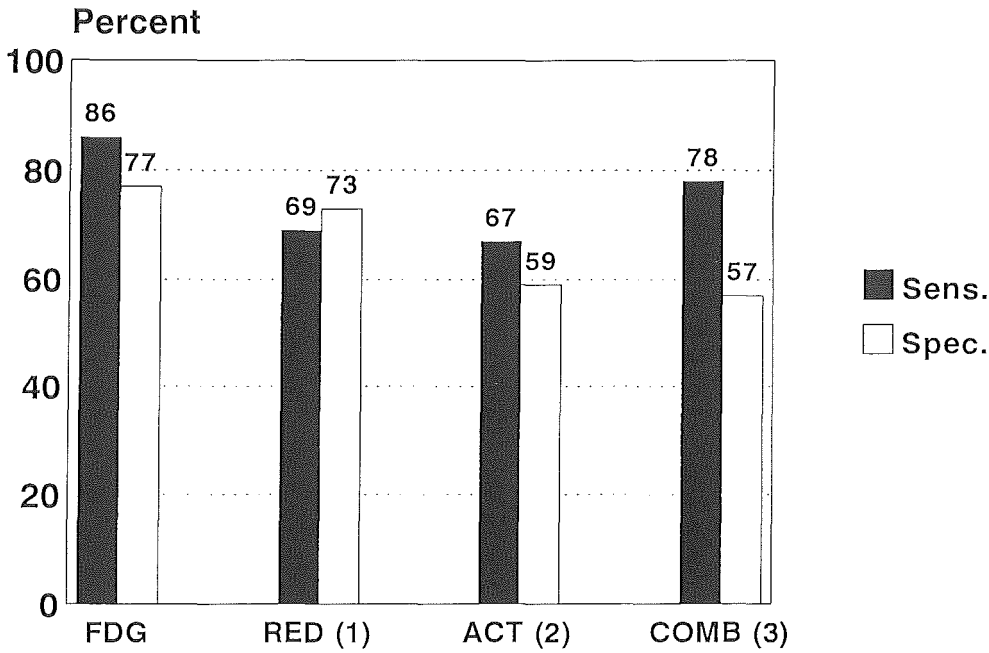

Figure 5 The sensitivities and specificities of FDG and rest-redistribution ^{201}Tl SPECT for the prediction of functional recovery are presented. For ^{201}Tl 3 approaches are presented: 1) significant redistribution (RED), 2) >75% ^{201}Tl activity at late imaging (ACT), 3) the combination of both viability criteria (COMB).

Discussion

This study expands the earlier studies with FDG SPECT [13-15] and demonstrates that quantitative FDG SPECT can accurately predict reversibility of regional contractile function after revascularization. The data suggest that patients who are likely to improve global LV function after revascularization can also be identified by this method. In contrast, rest-redistribution ^{201}Tl SPECT demonstrated a lower accuracy for the prediction of functional recovery in a head to head comparison with FDG SPECT.

In the present study one third of the dysfunctional myocardium improved its contractile function after revascularization. These segments demonstrated either normal perfusion, possibly representing repetitive stunning,[2] or a FDG-perfusion

mismatch likely to represent hibernation.[1] The majority of segments without functional improvement showed a FDG-perfusion match suggesting scar tissue.[4,5] The results obtained with FDG SPECT are in line with previous results obtained with FDG PET. In FDG PET studies sensitivity ranged from 71% to 100% (mean 88%) in predicting functional recovery, whereas specificity ranged from 38% to 86% (mean 74%).[34]

Sensitivity and specificity of FDG SPECT are not different in the subgroup of patients with severely depressed LV function (LVEF $\leq$30%), in whom prediction of functional recovery has the most clinical relevance. Patients with 3 or more dyssynergic but viable segments on FDG SPECT are likely to improve global LV function. These results are also valid for the subgroup with LVEF $\leq$30%. This finding corroborates previous data[6,12,22] and emphasizes that a substantial amount of viable myocardium is conditional for establishing improvement of global LV function after revascularization.

Although absence of viable myocardium was highly predictive for absence of recovery after revascularization, the presence of viable myocardium was less predictive (positive predictive value of 63%) for recovery of regional contractility. Recently vom Dahl et al described comparable results using FDG PET.[12] Several factors may have accounted for the lack of recovery of segments viable on FDG SPECT. It has been demonstrated that morphological degeneration occurs in viable myocytes before actual cell death takes place.[35,36] Marwick et al suggested that, despite increased FDG uptake, some segments may contain myocytes that are too severely injured to recover.[9] In addition an area with a mixture of viable myocytes and necrotic myocardium may result in a FDG-perfusion mismatch pattern. However, if the amount of viable cells in the area is relatively low, the segment may not improve in function after revascularization. Furthermore attempted revascularization may not be completely successful. Post-interventional reocclusion may have lead to incomplete recovery in contractile function in segments that were viable on FDG SPECT. Finally deterioration of viable myocytes in necrosis may have occurred silently preventing recovery in function even after adequate revascularization.

The lower specificity of FDG SPECT in hypokinetic segments is in agreement with PET literature.[12] The predominance of normal myocytes with

normal ^{201}Tl and FDG uptake in these hypokinetic regions may obscure uptake defects of small islands of nonviable cells, providing a false positive SPECT result. Since in clinical practice the issue of myocardial viability is mainly relevant in severe contraction abnormalities, this is not an important limitation of the technique.

^{201}Tl stress-redistribution-reinjection and ^{201}Tl rest-redistribution have been used extensively to detect viable myocardium.[21,22] Several studies have addressed the value of ^{201}Tl rest-redistribution for the prediction of improvement of regional myocardial dysfunction after revascularization.[20,22-24] The mean sensitivity and specificity for the prediction of functional recovery in these studies were 88% (range 44% to 95%) and 51% (range 31% to 88%) respectively. In the present study sensitivity varied from 67% to 78% dependent on which criterium was used (^{201}Tl redistribution, ^{201}Tl activity or the combination). Specificity ranged from 57% to 73%. However, FDG SPECT consistently showed a higher diagnostic accuracy than rest-redistribution ^{201}Tl SPECT.

The criteria for viability on ^{201}Tl rest-redistribution imaging included normal perfusion, substantial redistribution and ^{201}Tl activity on the late image. Previous studies generally use a cut-off level of 50% of ^{201}Tl activity.[21] We determined an optimal cut-off level of 75%. The difference between these levels may have resulted from the fact that in all previous studies 180° imaging was performed, whereas we used 360° imaging. Previously it has been reported that the 360° approach results in a lesser reduction of activity in ^{201}Tl defects as compared to 180° imaging.[37] In addition normalization to normal reference values leads to less severe defects in comparison with normalization to maximal ^{201}Tl activity.[20,22]
The use of a 180° versus a 360° orbit remains an issue of controversy.[38] In a comparative study, Go et al have demonstrated that 180° data sampling results in more false-positive segmental perfusion abnormalities as compared to 360° data sampling.[39] In addition, geometric distortion is reduced using 360° data sampling.[40] With the newer generation of multi-headed SPECT systems 360° data sampling does not result in longer acquisition time and is therefore recommended.[41]
The reduction of ^{201}Tl uptake on the early image was not significantly different in segments with or without improvement. It demonstrates that perfusion alone is unable to discriminate between viable and nonviable segments. Segments with a

perfusion defect demonstrating improved contractility after revascularization showed significant increased FDG uptake and redistribution of ^{201}Tl. These segments may represent hibernating myocardium, defined as myocardium with chronically decreased perfusion at rest.[1] The level of ^{201}Tl activity on the late image was significantly higher in segments that improved, which is in line with other studies.[20,22] Although myocardial viability can be demonstrated by both ^{201}Tl redistribution and increased FDG uptake, FDG activity was much more increased in the present study. This difference is probably due to different mechanisms of uptake of the two tracers. Since FDG uptake is able to exceed FDG uptake of normal myocardium (absolutely increased FDG uptake), ^{201}Tl uptake at redistribution may only reach the level of normal myocardium. Thus, the FDG "signal" may be more discriminative as compared to the ^{201}Tl redistribution "signal".

Methodological considerations

Early resting ^{201}Tl SPECT was used to measure regional perfusion since regional FDG uptake needs to be compared with regional perfusion. Melin and coworkers[19] demonstrated that initial myocardial uptake of ^{201}Tl was proportional to regional perfusion (determined with microspheres) even under ischemic conditions. The FDG SPECT study was performed during hyperinsulinemic euglycemic clamping. The clamping technique results in superior image quality,[42] particularly in patients with diabetes mellitus.[43,44] In addition, the clamping technique minimizes regional inhomogeneity in myocardial FDG uptake.[45] Hariharan et al[46] recently emphasized that only under steady-state conditions uptake and retention of FDG in the myocardium is linearly related to glucose utilization. For the FDG SPECT approach the criteria for viability were either normal perfusion or increased FDG uptake in ^{201}Tl perfusion defects. ^{201}Tl has lower photon energy than FDG. This may lead to differences in attenuation especially in the inferoseptal region of the myocardium. However we did not use attenuation correction. In normal volunteers we previously described no differences between tracer activities in various regions of the myocardium.[14] The normalization to normal reference values of ^{201}Tl and FDG reduces the effects of attenuation. In the present study we demonstrated that sensitivity and specificity for the detection of recovery were comparable in anterior, lateral and apical regions versus inferior and

septal regions.

The spatial resolution of SPECT is inferior to PET. Potentially, SPECT may not be able to detect small areas with increased FDG uptake. Its clinical relevance however is uncertain. PET studies have already demonstrated that a substantial amount of viable myocardium is a prerequisite for improvement of global LV function.[6,12,22]

Limitations

In this study improvement of regional myocardial function after revascularization was used as the gold standard for myocardial viability. Although revascularization reports were carefully reviewed it is possible that inadequate revascularization has occurred. Graft or vessel patency was not evaluated by repeated coronary angiography. Furthermore functional recovery may have been incomplete at the time of follow-up echocardiography. However these potential limitations may have affected both techniques equally.

Quantitative measurement of systolic wall thickening by MRI may allow more precise comparison between contractile function and quantitative SPECT data.[47] However we visually analyzed the echocardiograms.

Clinical implications

The results of the present study validate the use of FDG SPECT in the identification of potentially reversible wall motion abnormalities. Since FDG SPECT appears capable of determining the likelihood of functional recovery, it may lead to a more widespread use of this technique. It may support the clinician in selecting the appropriate treatment for patients with advanced LV dysfunction due to coronary artery disease.

Although FDG PET has been succesfully used in this clinical setting, PET is not widely available for routine clinical use. FDG SPECT therefore may contribute to a more routine use of FDG imaging for viability studies, if 511 keV collimators are available and distribution of FDG can be optimalized.

Conclusions

This study demonstrates the ability of FDG SPECT to predict functional

outcome of revascularization procedures on LV dysfunction. In contrast a direct comparison between FDG and rest-redistribution ^{201}Tl SPECT revealed a lower predictive value of the latter technique. Since gamma cameras are widely available, FDG SPECT may contribute to a more routine use of FDG imaging for studying myocardial viability.

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Chapter 9

Prediction of Improvement of Ventricular Function After Revascularization: Quantitative ^{18}F-Fluorodeoxyglucose Single-Photon Emission Computed Tomography Versus Low-Dose Dobutamine Echocardiography

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Abstract

Aims

To compare ^{18}F-fluorodeoxyglucose (FDG) imaged with single-photon emission computed tomography (SPECT) and low-dose dobutamine echocardiography (LDDE) in predicting improvement of regional and global left ventricular (LV) function after coronary artery bypass graft surgery (CABG).

Methods and results

Thirty patients with regional wall motion abnormalities (mean ejection fraction 32 ± 19%) who underwent uncomplicated CABG were studied with LDDE (5 and 10 μg/kg/min) and ^{201}Thallium (^{201}Tl)/FDG SPECT prior to surgery. For comparative analysis, a 13-segment model was used. Reversibility of wall motion abnormalities during dobutamine infusion on echo as well as normal perfusion or a relatively increased FDG uptake in perfusion defects (mismatch) in dyssynergic segments on SPECT were considered predictive for post-operative improvement. After CABG the LV function was reassessed with a rest echocardiogram at 3 months follow-up. Regional wall motion improved in 62 / 168 (37%) revascularized segments. LDDE showed a sensitivity of 89% and specificity of 82% in predicting post-operative functional outcome whereas ^{201}Tl/FDG SPECT had a sensitivity and specificity of 84% and 86%. In patients with ≥2 viable segments on either technique, the wall motion score index, a derivative of global LV function, improved significantly after follow-up.

Conclusion

Both ^{201}Tl/FDG SPECT and LDDE seem valuable in predicting improvement of LV function after CABG.

Introduction

Assessment of myocardial viability is relevant for the optimal treatment of the rising number of patients with left ventricular (LV) dysfunction due to significant coronary artery disease. It has been demonstrated that in some patients, coronary artery bypass grafting (CABG) can improve LV function, functional state and survival even in the presence of severe LV dysfunction.[1-3] The presence of

residual viability in dyscontractile myocardial tissue has been used to explain improvement of LV function after revascularization. However it is likely that a "critical mass" of viable tissue is necessary for functional recovery to occur. The identification of myocardial regions with high and low probability of functional improvement after revascularization is important for the decision to perform revascularization procedures in individual patients with severe wall motion abnormalities and reduced global LV function, as an alternative to heart transplantation.[4]

Among the available techniques, positron emission tomography (PET) of myocardial perfusion and metabolism (using ^{18}F-fluorodeoxyglucose (FDG) is considered the most accurate method for the identification of viable myocardium.[5-15] This technique is able, by detecting normal perfusion, perfusion-metabolism mismatches or matches, to predict reversibility of regional as well as global LV function.[5-7] However high costs and limited availability restrict the use of this technique for clinical routine.

To respond to the increasing demand for viability studies, other techniques have been proposed, including imaging myocardial FDG uptake with single-photon emission computed tomography (SPECT) using special 511 keV collimators,[16-20] and low-dose dobutamine echocardiography (LDDE).[21-25] These techniques are attractive from a clinical point of view, but they elucidate different cellular mechanisms of viability. The present study was designed to compare ^{210}Thallium (^{201}Tl)/FDG SPECT and LDDE in predicting improvement of regional and global LV function after uncomplicated CABG. Post-operative improvement of LV function was determined with a rest echocardiogram 3 months after surgery.

Methods

Patients and study protocol

Thirty patients with stable LV dysfunction (ejection fraction ranging from 13% to 50%; 4 patients with an ejection fraction >45%) were prospectively enrolled in the present study prior to scheduled CABG. They fulfilled the following criteria: 1) history of myocardial infarction before the study, 2) regional dyssynergy on resting echocardiogram, 3) no recent episodes of unstable angina, 4) no significant valvular disease. All had undergone coronary arteriography and contrast ventriculography prior to the study. The decision to revascularize was based on

clinical criteria and was taken before study entry. The results of the SPECT and LDDE studies were withheld from the physicians managing the patients. Adequate revascularization of a dyssynergic segment was considered achieved if upon review of the operative report and the pre-operative coronary arteriogram, bypass grafts were placed to the major branches supplying the dyssynergic segments. Each patient gave informed consent to the study protocol that was approved by the ethical committees of the participating hospitals.

All patients underwent ^{201}Tl/FDG SPECT and LDDE within 1 week without intervening cardiac events. Beta-blockers were withdrawn 36 hours before LDDE; all other cardiac medication (e.g. calcium antagonists, nitrates and/or ACE inhibitors) were continued during both tests. To assess recovery of function, resting two-dimensional echocardiograms were obtained before and 3 months after CABG.

^{201}Thallium/FDG SPECT

First, myocardial perfusion was delineated using an early resting 201Tl/ SPECT, as described previously.[26] A single dose of 111 MBq ^{201}Tl-chloride was administered intravenously and imaging was performed 10 min after injection. Delayed ^{201}Tl images were not acquired. The FDG SPECT study was performed on the same day during hyperinsulinemic euglycemic clamping to standardize metabolic conditions,[27] and guarantee good image quality even in patients with diabetes mellitus.[28] FDG (185 MBq) was injected after 60 min of clamping; another 45 min was allowed to obtain optimal myocardial FDG uptake.[29]

Data acquisition was performed with a large-field-of-view rotating dual head gamma camera (ADAC Laboratories, Milpitas CA), equipped with a low-energy high-resolution collimator for the ^{201}Tl study and equipped with 511 keV collimators (van Mullekom, Nuclear Fields, Boxmeer, The Netherlands) for the FDG study. The specific details of these collimators have been described previously.[30] The dual head gamma camera system was rotated over 180° around the patient. From the raw scintigraphic data 6 mm-thick (1 pixel) transaxial slices were reconstructed by filtered back projection using a Hanning filter (f_c = 0.63 cycle/cm). Slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis projections perpendicular to the heart-axis.

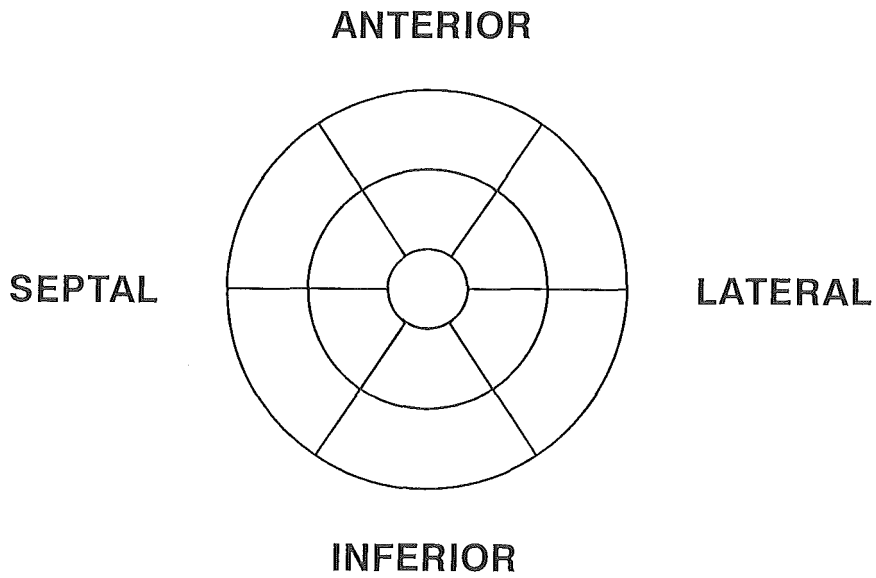

Figure 1 The 13-segment model used for the analysis of both the SPECT and echocardiographic studies is presented. The myocardium is divided into 1 apical segment, 6 distal and 6 basal segments (anterior, anterolateral, posterolateral, inferior, inferoseptal and anteroseptal).

Quantitative SPECT analysis

Quantitative analysis was performed as described previously.[16] Briefly, circumferential count profiles (60 radii, highest pixel/radius) from ^{201}Tl- and FDG short-axis slices were generated and displayed in a polar map. The polar maps were divided into 13 segments, dividing the myocardium into 1 apical, 6 distal and 6 basal segments (Figure 1). The segment with the highest ^{201}Tl-uptake was considered as normal myocardium. The mean activity of this segment was adjusted to a normal database,[16,17] and all other segments were adjusted correspondingly. For FDG SPECT, the same adjustment procedure as for ^{201}Tl was followed, except that a separate normal database for FDG was used.[16,17]

A perfusion defect was considered present if the segmental ^{201}Tl activity was below 2 SD of normal. In the segments with a perfusion defect the mean FDG and

^{201}Tl activities were compared. Dyssynergic segments with either normal perfusion or a 7% increased FDG uptake in perfusion defects (perfusion-metabolism mismatch) were considered myocardial regions with a high probability of functional improvement after revascularization. In contrast, dyssynergic segments with a ^{201}Tl perfusion defect without increased FDG uptake (perfusion-metabolism match) were classified as having a low probability of functional recovery. The 7% cutoff value was defined previously using ROC analysis in a different group of patients undergoing revascularization.[31]

For analysis on a patient basis, patients were considered to have the ability to recover functionally ("recoverable") if $\geq$2 adjacent dyssynergic segments showed normal perfusion or a mismatch pattern on ^{201}Tl/FDG SPECT.

Low-dose dobutamine echocardiography

A two-dimensional transthoracic echocardiogram in standard apical and parasternal views and a 12-lead ECG were recorded at rest. Dobutamine was infused by a volumetric pump through an antecubital vein at doses of 5 and 10 μg/kg/min, for 5 min at each dose. Continuous monitoring of the echocardiogram was obtained during the test, and recorded on video tape at the last minute of both stages.

The echocardiographic images were also digitized (Prevue-III, Nova-Microsonics or Vingmed CFM 800) and displayed in quad-screen format to facilitate the comparison of rest and dobutamine images. A 3-lead ECG was continuously monitored and a 12-lead ECG was recorded every minute. Blood pressure was measured by sphygmomanometer at each stage.

Analysis of echocardiograms

The interpretation of echocardiograms was performed by two experienced observers, blinded to the clinical data and SPECT results. In case of disagreement, a third observer reviewed the study and a majority decision was achieved. The stress- and post-operative resting echocardiograms were interpreted within 1 week after acquisition. Post-operative resting echocardiograms were analyzed without knowledge of the LDDE results. For analysis of echocardiograms we used a 13-segment model to allow comparison with the 13 segments of the SPECT polar maps.[16]

Wall motion of every segment, including wall thickening, was scored with a 4-point scoring system (0 = normal, 1 = mildly hypokinetic, 2 = severely hypokinetic, 3 = akinetic or dyskinetic). We defined a segment as severely hypokinetic in the presence of minimal wall thickening (<2mm) with a limited inward motion; as akinetic in the absence of systolic wall motion and thickening, and as dyskinetic in the presence of systolic outward motion with thinning. Wall thickening was primarily utilized for the classification of wall motion, pre-empting the problem of post-operative paradoxical septal motion. Additionally, in order to reduce the confounding effect of tethering, segmental wall thickening was analyzed frame by frame during the first half of systole.

The LDDE studies were analyzed using the digitized rest and dobutamine images, displayed in a quad-screen format and also by reviewing the images recorded on video tape. Dyscontractile regions were considered to have a high probability of functional improvement after revascularization when wall motion improved by at least one point of the scoring system during the infusion of low-dose dobutamine. A lack of improvement or direct worsening in wall motion were considered a low probability of functional recovery.

For analysis on a patient basis, patients were considered to have the ability to recover functionally ("recoverable") if ≥2 adjacent dyssynergic segments showed improved wall motion during dobutamine infusion. Follow-up echocardiograms were compared with the corresponding pre-operative resting images, without knowledge of the dobutamine studies. For each segment, recovery of function was defined as an improvement of one or more grades.

We previously reported a low level of inter- and intra-observer variability for the classification of resting wall motion (agreement 84% and 87%) and the response to low-dose dobutamine (agreement 92% and 94%) in a different but comparable patient group.[22] For individual patients, functional recovery was defined as an improvement of segmental wall motion score after revascularization in ≥2 adjacent segments. Finally, a wall motion score index (WMSI) was calculated from the pre-operative and post-operative resting echocardiograms to evaluate change in global LV function. WMSI was defined as the sum of the scores of each segment divided by the total number of segments analyzed.

Statistical analysis

Continuous data are expressed as means ± standard deviation (SD). A paired or unpaired Student's *t*-test was used when appropriate. Univariate analysis for categorical variables was performed using the chi-square test with Yates' correction. Sensitivity, specificity, positive and negative predictive values were based upon their standard definitions. McNemar's test was used to compare the sensitivity and specificity of ^{201}Tl/FDG SPECT and LDDE in the prediction of functional recovery. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

Results

Characteristics of the study group

The study group comprised 30 patients (25 men, 5 women) with stable coronary artery disease and regional LV dysfunction who underwent an uncomplicated CABG procedure. The demographic, clinical and angiographic data are summarized in Table 1.

Of the 390 segments, 388 were visualized by resting echocardiography. Of these segments 212 (55%) had normal wall motion and 176 (45%) showed abnormal wall motion at rest. The mean number of abnormal segments per patient was 5.6 ± 3.5. Eight dyssynergic segments were excluded from post-operative evaluation due to inadequate revascularization. Thus, 168 segments were available for serial analysis. Sixty-six (39%) dyssynergic segments were classified as mildly hypokinetic and 102 (61%) as severely dyssynergic (33 severely hypokinetic and 69 a- or dyskinetic).

Post-operative results

At 3 months follow-up 62 (37%) of the 168 dyssynergic segments showed an improvement of wall thickening and motion. The improvement was observed in 35 (53%) of the 66 mildly hypokinetic segments and in 27 (26%) of the 102 severely dyssynergic segments (in 16 severely hypokinetic and 11 a- or dyskinetic segments; $p < 0.01$ severely dyssynergic versus mildly hypokinetic segments). The mean WMSI decreased significantly from 0.90 ± 0.48 to 0.72 ± 0.44 ($p < 0.05$). Patient-by-patient analysis revealed improvement of wall motion in ≥2 adjacent

Table 1 Baseline characteristics of the study population

	n = 30
Gender (M/F)	25 / 5
Age (yr) (mean ± SD)	61 ± 11
Diabetes mellitus	4
Previous CABG / PTCA	5 / 1
Previous myocardial infarction	30
< 1 month	1
> 1 month	19
Q / non-Q wave	20 / 10
Effort angina (%)	24 (80)
Effort dyspnea (%)	16 (53)
Coronary arteriography	30
1 vessel disease (%)	7 (23)
2 vessel disease (%)	6 (20)
3 vessel disease (%)	17 (57)
LVEF (%) (mean ± SD)	35 ± 10

CABG: coronary artery bypass grafting, LVEF: left ventricular angiographic ejection fraction, PTCA: percutaneous transluminal coronary angioplasty.

segments in 15 of the 30 patients. None of the patients complained of residual angina pectoris at follow-up.

^{201}Tl/FDG SPECT

^{201}Tl/FDG SPECT identified a high probability of recovery in 52 of the 62 (84%) segments showing improved wall motion after revascularization. A mismatch pattern was present in 24 of these 52 segments and 28 had normal

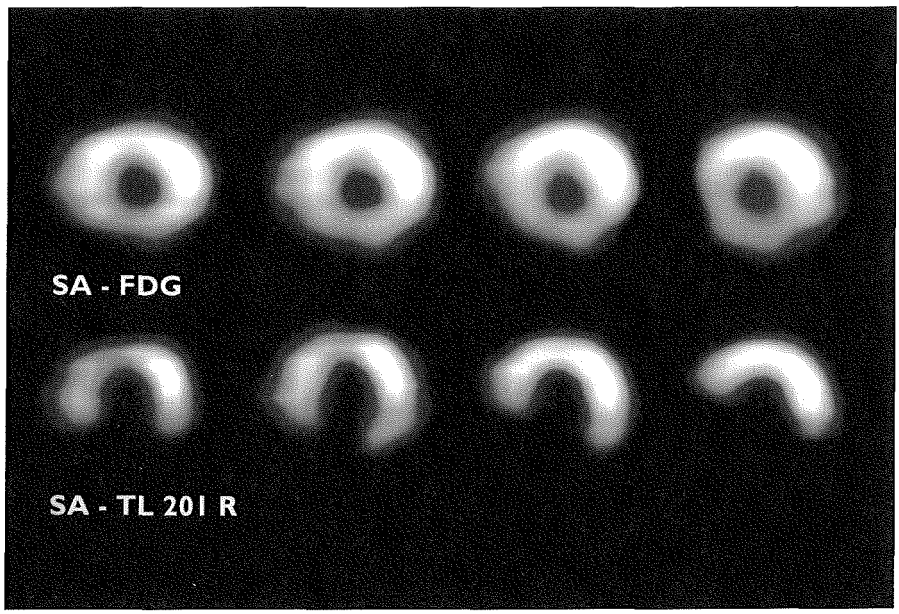

Figure 2 Corresponding series of short axis FDG- (top) and ^{201}Tl slices (bottom) demonstrating a perfusion-metabolism mismatch in the infero-septal region.

perfusion. An example of a perfusion-metabolism mismatch at SPECT is shown in Figure 2. In contrast, ^{201}Tl/FDG SPECT identified 91 of the 106 (86%) segments failing to improve as a low recovery probability. These results yielded a sensitivity of 84% and a specificity of 86% with a positive predictive value of 78% and a negative predictive value of 90% for ^{201}Tl/FDG SPECT to predict functional recovery on a segmental basis after revascularization (Figure 3).

When analyzed patient-by-patient, ^{201}Tl/FDG SPECT correctly identified 14 of the 15 (93%) patients showing post-operative recovery. Conversely, SPECT correctly identified 13 of the 15 (87%) patients without post-operative recovery. In patients with ≥ 2 viable segments with a high recovery probability on ^{201}Tl/FDG SPECT, the WMSI decreased significantly from 0.92 $\pm$ 0.54 before to 0.64 $\pm$ 0.46 after CABG ($p < 0.01$). Conversely, in patients with ≤ 1 viable segment, the

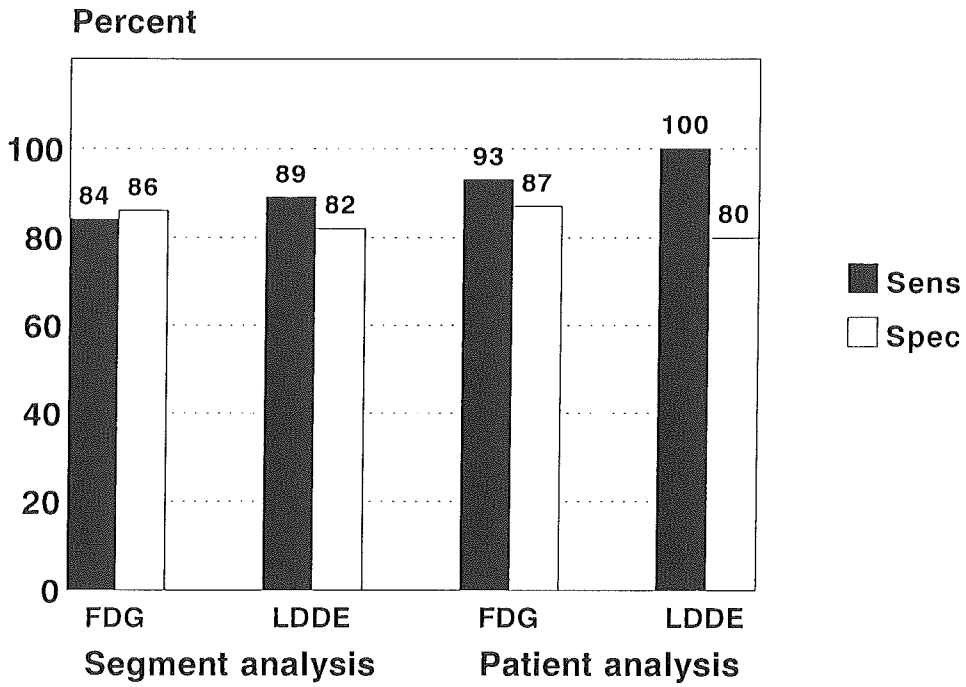

Figure 3 Bar graph showing the sensitivity and specificity of ^{201}Tl/FDG SPECT and LDDE for recovery of contractile function after CABG, both on a segmental and on a patient basis.

WMSI remained unchanged (0.87 ± 0.39 versus 0.81 ± 0.39, NS).

The diagnostic accuracy of ^{201}Tl/FDG SPECT was also determined according to the severity of the wall motion abnormalities at baseline (Figure 4). In mildly hypokinetic segments, the sensitivity and specificity were 86% and 74% respectively, whereas in severely dyssynergic segments the sensitivity and specificity were 81% and 91%.

Low-dose dobutamine echocardiography

No complications occurred during the tests. Heart rate increased from 73 ± 15 beats/min at rest to 86 ± 14 beats/min during the infusion of 10 μg/kg/min

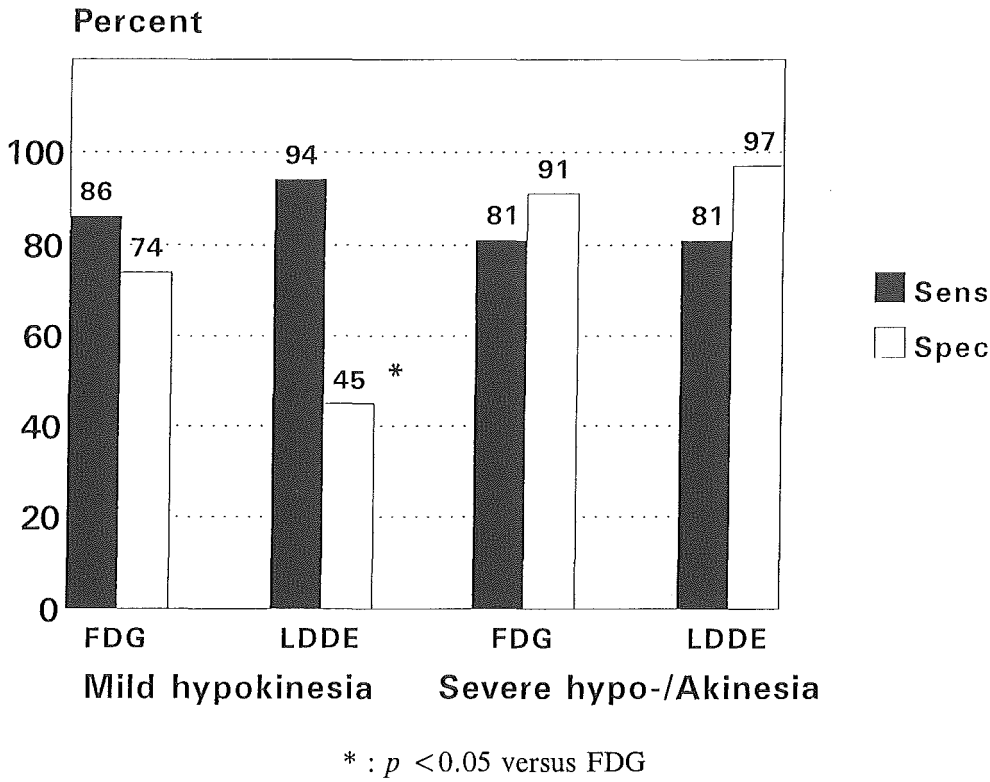

Figure 4 Bar graph showing the sensitivity and specificity of ^{201}Tl/FDG SPECT and LDDE for recovery of contractile function after CABG, in segments with mild hypokinesia versus severe dyskinesia.

dobutamine ($p < 0.01$). LDDE revealed a contractile reserve in 55 of the 62 (89%) segments showing improved wall motion after CABG. On the other hand, LDDE identified 87 of 106 (82%) segments failing to improve as a low recovery probability. Consequently, LDDE had a sensitivity of 89% and a specificity of 82% with a positive predictive value of 74% and a negative predictive value of 93% to predict recovery of regional function after revascularization (Figure 3).

In individual patients, LDDE had a sensitivity of 100% (15/15) and a specificity of 80% (12/15) to predict post-operative functional improvement. In patients with ≥ 2 viable segments on LDDE, the WMSI decreased significantly

from 1.00 ± 0.54 before to 0.70 ± 0.50 after CABG ($p < 0.01$). Conversely, in patients with ≤1 viable segment, the WMSI remained unchanged (0.75 ± 0.31 versus 0.74 ± 0.31, NS).

Similar to ^{201}Tl/FDG SPECT, the diagnostic accuracy of LDDE was determined according to the severity of wall motion abnormalities prior to surgery. In mildly hypokinetic segments the sensitivity and specificity were 94% and 45% respectively. In severely dyssynergic segments the sensitivity and specificity were 81% and 97%.

Comparison between ^{201}Tl/FDG SPECT and LDDE

The agreement between ^{201}Tl/FDG SPECT and LDDE on a segmental basis was 82%. Both techniques identified 54 segments as having a high recovery probability ("recoverable") and 84 segments as having a low recovery probability. In severely dyssynergic segments, the sensitivity and specificity to predict post-operative functional outcome were comparable for ^{201}Tl/FDG SPECT and LDDE (Figure 4). However, in mildly hypokinetic segments the specificity of LDDE was significantly less in comparison with ^{201}Tl/FDG SPECT (45% versus 74%, $p < 0.05$).

Discussion

To select the most appropriate treatment for patients with advanced LV dysfunction, a correct identification of the amount of potentially reversible (viable) dysfunctional myocardium is important for the prediction of improvement of global LV function after coronary revascularization. At present many techniques are available for the detection of viable myocardium.[4] However, not many studies have compared the different techniques for assessing the likelihood of improvement of regional and global LV function after successful revascularization.

The present study represents a head to head comparison of two recently developed techniques for the identification of wall motion abnormalities with low or high probability of post-operative recovery, ^{201}Tl/FDG SPECT and LDDE. The main findings of the present study are as follows. ^{201}Tl/FDG SPECT and LDDE have similar excellent accuracies for the prediction of post-operative improvement of regional LV function, particularly in severely dyssynergic

segments. In mildly hypokinetic segments the specificity of both techniques is less in comparison with severe dysfunctional segments. Particularly LDDE overestimates the probability of post-operative functional recovery in segments with mild hypokinesia (specificity 45% versus 74% with SPECT, $p < 0.05$). On a patient basis, both ^{201}Tl/FDG SPECT and LDDE provide in 90% correct information regarding post-operative functional outcome.

Distinction between viability and the potential of functional recovery

It is important to distinguish the concept of metabolically viable myocardium from the ability of the myocardium to recover its mechanical ventricular function. Although mildly hypoperfused dyssynergic myocardium with a matched reduction in FDG uptake represents residual viablility (viable match), it is less likely to recover functionally after adequate revascularization.[6] By differentiating between perfusion-metabolism match or mismatch, PET has demonstrated adequate prediction of recovery of regional and global LV function after revascularization.[5,8-15]

LDDE versus FDG imaging

Functional and metabolic imaging reflect different physiologic phenomena of myocardial viability. Both LDDE as well as FDG imaging have attracted clinicians. The adrenergic stimulus initiated by dobutamine infusion leading to increased contractility represents the physiologic rationale of LDDE. By recruiting a critical mass of dormient but viable dyfunctional myocytes, echocardiography is capable of detecting viable myocardium with a high likelihood of functional recovery after adequate revascularization. Myocardial FDG uptake on the other hand reflects metabolic activity, independent of contractility. Since glucose uptake is increased in ischemically jeopardized but viable myocardium it is possible to detect myocardium with the potential to recover its contractile function.[5-15]

In the present study, a surprisingly good agreement between the functional and metabolic imaging technique was found. This can be explained by the criteria used, since a viable match with ^{201}Tl/FDG SPECT was considered as a low probability of functional recovery. Previous studies have reported the relation between ^{201}Tl uptake, contractile response to dobutamine and post-operative

recovery.[22,32] Although ^{201}Tl SPECT detected myocardial viability (defined as >50% uptake) more frequently,[32] it also seemed to overestimate functional recovery after CABG compared to LDDE.[22] Our findings are supported by a recent comparative study between LDDE and PET in similar patients.[33] The extent of dobutamine-induced contractile reserve appeared to compare less closely with the total extent of viable myocardium than with the extent of perfusion-metabolism mismatch.

Mildly versus severely dyssynergic segments

In hypokinetic segments both techniques, but especially LDDE, seems to overestimate functional recovery after revascularization. These segments are likely to contain normal myocardium, subendocardial scar and/or viable but dysfunctional myocardium. If relatively little viable tissue is present, dobutamine challenge may stimulate normal myocardium to a hyperkinetic response simulating a positive test for viability. It is conceivable that combining low with high dose dobutamine infusion could have increased the specificity of stress echocardiography for predicting functional recovery.[23] Using the entire dose- range some segments may have exhibited a biphasic response (jeopardized but viable) with high probability of recovery, whereas other segments may have shown continuous enhancement of wall thickening (non-jeopardized). However our patients only underwent a low dose dobutamine infusion. Furthermore, since predominance of normal myocytes with normal ^{201}Tl uptake may obscure uptake defects of small islands of nonviable cells, this may have led to some false positive SPECT results in mildly hypokinetic segments.

FDG SPECT

So far the study of myocardial FDG uptake has mainly been confined to the availability of PET.[5-15] Recently, the development of a special collimator made it possible to study myocardial FDG uptake with SPECT as well.[16-20] For clinical purposes, SPECT imaging may provide a widely available approach for the detection of myocardial viability. Some technical features of FDG imaging, applied in our protocol should be underscored. In order to optimize and standardize metabolic conditions, we used the hyperinsulinemic euglycemic clamping technique. These

metabolic conditions lead to enough exogenous glucose uptake for optimal target-to-background ratio resulting in good diagnostic image quality,[27] and furthermore enhance a more homogenous FDG uptake.[34] Moreover, Hariharan et al have recently demonstrated that variations in metabolic and hormonal circumstances can affect myocardial FDG uptake.[35] The more widespread used alternative approach employing oral glucose loading may result in a more variable metabolic milieu and was therefore not chosen.

In this study we have compared regional FDG uptake with perfusion assessed with ^{201}Tl. Although these tracers have different photon energies, we have recently compared regional FDG and ^{201}Tl uptake in normal individuals.[17] In that study, no significant differences between uptake of the 2 tracers could be demonstrated in any of the different myocardial regions. However, influence of photon attenuation, particularly on the ^{201}Tl images, cannot be ruled out. A future study using our protocol in combination with attenuation correction is warranted.

Previous studies

In comparison to the PET literature, relying on comparable methodologies, similar sensitivities and specificities in patients undergoing revascularization were reached as compared to our FDG SPECT results. In the reported 194 patients derived from 9 studies PET showed a mean sensitivity of 87% and a mean specificity of 77%.[5,8-15] Previous studies have shown that pre-operative inotropic reserve predicts improvement of wall motion abnormalities after revascularization,[21-25] and have demonstrated a sensitivity ranging from 74% to 95% and a specificity ranging from 73% to 95%. The data obtained in our study are in line with these results.

Limitations

In the present study graft patency was not assessed after revascularization. Reocclusion may have accounted for the failure of some viable segments to recover in contractile function, particularly in the segments that were viable both on LDDE and FDG. Recent data suggest that jeopardized myocardium, a combination of myocardial viability and inducible ischemia, is more likely to recover after revascularization than viable myocardium which is not in jeopardy. However we

did not perform high dose dobutamine stress testing and cannot comment on the so called "biphasic response". We have not noted this response during the LDDE studies. Functional improvement was arbitrarely assessed 3 months after surgical revascularization. It cannot be excluded that additional functional improvement may occur later as was already suggested.[36]

Conclusion

LDDE and ^{201}Tl/FDG SPECT imaging are both valuable methods for the prediction of improvement of regional and global LV function after CABG. Both methods are more and more available and may be useful techniques for the routine detection of potentially reversibly dysfunctional viable myocardium.

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Chapter 10

Biphasic Response to Dobutamine Predicts Recovery of Global Ventricular Function After Surgical Revascularization

Implications of Time Course of Recovery on Diagnostic Accuracy

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Abstract

Background

This study sought to evaluate the time course of recovery of left ventricular dysfunction in stable patients and its implications on the accuracy of dobutamine echocardiography to predict recovery after surgical revascularization.

Methods

Consecutive patients with chronic ischemic left ventricular dysfunction scheduled for elective surgical revascularization were prospectively selected. They underwent dobutamine echocardiography (5 to 40 μg/kg/min) and radionuclide ventriculography both preoperatively and at 3 month follow-up. At 14 months another evaluation of ventricular function was obtained. To analyze echocardiograms a 16 segment model and a 5-point scoring system was used. Dyssynergic segments were considered likely to improve in presence of a biphasic contractile response to dobutamine. Improvement of global function was defined as a $\geq 5\%$ increase in left ventricular ejection fraction.

Results

Of the 61 patients, ejection fraction improved in 12 at 3 months and in a total of 19, (i.e. 7 more), at late (14 month) follow-up (from 32 $\pm$ 8% to 42 $\pm$ 9%, $p < 0.0001$). A biphasic response was predictive for recovery in 118/186 (63%) segments at 3 months and in 140/186 (75%) at late follow-up. Other responses were highly predictive for non-recovery (92%). In mildly hypokinetic segments the positive predictive value of the test was significantly lower compared to severely dyssynergic segments (67% (95% CI, 59% to 75%) versus 90% (95% CI, 83% to 97%) at late follow-up). The sensitivity and specificity for recovery of global function on a patient basis (≥ 4 biphasic segments) were 89% and 81% at late follow-up.

Conclusions

Serial post-operative follow-up studies demonstrate incomplete recovery of regional and global contractile function at 3 months. The diagnostic accuracy of dobutamine echocardiography to predict recovery depends on combining low and

high dobutamine dosages, severity of dyssynergy and the timing of evaluation.

Introduction

Coronary artery bypass grafting (CABG) can improve symptoms, prognosis and left ventricular (LV) function in selected patients.[1] The non-invasive identification of myocardial regions with high and low probability of functional improvement after revascularization is crucial for the decision to perform revascularization procedures in individual patients with multiple severe wall motion abnormalities.[2] Since the presence of viable myocardium favourably influences prognosis after revascularization,[3-6] these procedures may even serve as an attractive alternative to cardiac transplantation.

The contractile response of dyssynergic regions to "low-dose" dobutamine in conjunction with echocardiography has been proposed as a simple method for the assessment of residual viable myocardium capable of recovering its contractile function, both spontaneously in patients early after myocardial infarction[7-11] and after revascularization in patients with stable chronic ischemic heart disease.[12-16]

Recent data suggest that jeopardized myocardium, a combination of myocardial viability and inducible ischemia, is more likely to recover after revascularization than viable myocardium which is not in jeopardy.[16] However all previous studies using dobutamine echocardiography have been limited by the lack of an independent method to verify changes in ventricular function.[12-20]

The accuracy of predicting recovery of contractile function after revascularization depends on several factors such as the response to dobutamine both at low and high dose[16] and severity of baseline segmental dysfunction.[11,15] Furthermore it is unclear what the optimal timing is to evaluate recovery of contractile function after revascularization. Given the severity of structural changes observed in hibernating myocardium,[21,22] it is likely that recovery of function after revascularization is delayed for several months.

Therefore we designed a prospective study to evaluate 1) the accuracy of dobutamine echocardiography to predict recovery of regional and global LV dysfunction after successful CABG in patients with a wide range of chronic LV dysfunction, and 2) the time course of functional improvement after CABG using both serial echocardiographic - and radionuclide ventriculographic studies, and so

defining the optimal timing to determine the diagnostic value of dobutamine echocardiography in this clinical setting.

Methods

Patient enrollment

From January 1993 to April 1995, all patients with coronary artery disease and LV dysfunction at rest, who were scheduled to undergo CABG at the Thoraxcenter, were screened for enrollment in the study. The study protocol was approved by the Institutional Review Board. Inclusion criteria were symptoms of stable coronary artery disease, prior acceptance for elective surgical revascularization, ejection fraction (EF) of $<50\%$ on contrast ventriculography, and one or more abnormal contractile segments on preoperative (<3 weeks before operation) resting echocardiogram (16-segment left ventricular model). Furthermore a subsequent uneventful surgical revascularization procedure was required to proceed with the protocol. Exclusion criteria were unstable angina, recent myocardial infarction (<3 months), significant ($>50\%$) left main stem stenosis, (hemodynamically) significant valvular disease, poor echo quality, or the inability to obtain informed consent. Of the 89 preoperative eligible patients 28 were excluded. The reasons for exclusion were resection of infarcted areas in addition to myocardial revascularization in 13 patients, perioperative death in 6 (7%), perioperative nonfatal myocardial infarction in 2, poor echo quality in 3, inability to obtain informed consent in 2, death on the waiting list for surgery in 1 and death early in the follow-up (at 10 weeks) in 1 patient. Of the patients who died perioperatively, 2 deaths were due to pump failure and 4 due to perioperative myocardial infarction. Of the 61 patients finally included in the present study, 5 (8%) underwent CABG as an alternative to cardiac transplantation.

Study protocol

Each patient underwent a low and high dose dobutamine stress echocardiogram and a radionuclide ventriculography within the 3 weeks prior to surgery. All patients underwent uneventful isolated CABG (by definition). The decision to revascularize was based on clinical criteria. The results of the dobutamine stress echocardiographic and radionuclide studies were withheld from the physicians

managing the patients. Adequate revascularization of a dyssynergic segment was considered achieved if upon review of the operative report and the preoperative coronary arteriogram, bypass grafts were placed on the stenotic major branches supplying the dyssynergic segments. After the operation, patients were followed up to a maximum of 19 months. At 3 months follow-up both low and high dose dobutamine stress echocardiography and radionuclide ventriculography at rest were repeated. At 12 months follow-up a two-dimensional resting echocardiogram and a third radionuclide ventriculography were performed.

Dobutamine stress echocardiography

Before the test, patients were asked to discontinue ß-blockers for 36 hours. All other cardiac medication (e.g. calcium antagonists, nitrates and/or ACE inhibitors) were continued. The dobutamine stress test was performed as follows. A two-dimensional transthoracic echocardiogram in standard views and a 12-lead ECG were recorded with the patient at rest. Dobutamine was infused through an antecubital vein at dosages of 5 and 10 μg/kg/min, for 5 minutes at each dose (these 2 steps were considered as "low-dose"). Subsequently, 3 other steps from 20 to 40 μg/kg/min (3 minutes each) were added. Finally, atropine (up to 1 mg) was injected when 85% of the predicted maximal (men (220 - age) x 85%, women (200 - age) x 85%) heart rate had not been reached.[23]

A 3-lead ECG was monitored continuously, and a 12-lead ECG was recorded every minute. Cuff blood pressure was measured at each stage. The test was interrupted prematurely if 85% of the predicted maximal heart rate was reached or if severe chest pain, ST-segment deviation >2 mm, significant ventricular or supraventricular arrhythmia, systolic blood pressure fall of >40 mm Hg or any other intolerable side effect occurred during the test.

The echocardiogram was monitored throughout the test, and the last minute of each stage, including recovery, was recorded on video tape. The echocardiographic images were also digitized on optical disk [Vingmed CFM 800] or on floppy disk [Esaote Biomedica SIM 7000] and displayed side-by-side in quadscreen format to facilitate the comparison of images at rest and at various stages of the test.

Analysis of echocardiograms

The interpretation of echocardiograms was performed by 2 experienced observers who were blinded to the clinical, radionuclide, angiographic, and previous echocardiographic results of the individual patients. In case of disagreement, a third observer reviewed the study and a majority decision was achieved. The assessment was based on both the digitized images displayed in a quadscreen format and a review of the images recorded on the videotape. For analysis of wall motion, the left ventricle was divided into 16 segments as recommended by the American Society of Echocardiography.[24] The wall motion, including wall thickening, of every segment was semi-quantitated using a 5-point scoring system where 1 = normal wall motion and thickening, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic and 5 = dyskinetic. We defined a segment as severely hypokinetic in the presence of minimal wall thickening with very limited inward motion (during first half of systole); as akinetic in the absence of systolic wall motion and thickening and, whenever possible, confirmed by M-mode tracing; and as dyskinetic in the presence of systolic outward motion with thinning. Wall thickening was primarily utilized for the classification of wall motion, preventing the problem of postoperative paradoxical septal motion. Also, to reduce the confounding effect of tethering from adjacent segments, segmental wall thickening was analyzed only during the first half of systole.

During dobutamine infusion, abnormally contracting segments at rest were classified into 4 different patterns of contractile response: biphasic, defined as improvement at low-dose and worsening at peak stress; sustained improvement, defined as improvement at low-dose without further deterioration at peak stress; worsening, defined as direct worsening without any improvement at any stage; and no change, defined as unchanged wall motion abnormality throughout the test.

We previously reported a low level of inter- and intra-observer variability for the classification of resting wall motion (agreement 84% and 87%) and the response to low-dose dobutamine (agreement 92% and 94%) in a comparable patient group.[15] Myocardial ischemia was judged to be present when there was worsening by ≥ 1 of the segmental score. As previously reported, ischemia was not considered when akinetic segments at baseline became dyskinetic at stress

without improvement during low-dose dobutamine infusion.[25] Follow-up echocardiograms were compared with the correspondent preoperative resting images. The observers were blinded to the preoperative dobutamine results. For each segment, improvement of function was defined as a decrease of one or more grades. A change from dyskinetic to akinetic was not considered to be improved contractile function.

Radionuclide ventriculography

Equilibrium radionuclide ventriculography was performed at rest with the patient in supine position after intravenous administration of 555 MBq of ^{99m}technetium. Images were acquired with a small-field-of-view gamma camera (Orbiter, Siemens Corp., Iselin, NY, USA) oriented in the 45 degree left anterior oblique position with a 5-10 degree caudal tilt. The LVEF was calculated by an automated technique. Improvement of global LV function after revascularization was defined as an increase in LVEF by at least 5 points (e.g. from 30% to 35%).

Statistical analysis

Age, number of stenotic coronary arteries, LVEF, heart rate and systolic blood pressure are expressed as mean ± standard deviation. Differences within continuous variables over time were evaluated by analysis of variance (ANOVA) for repeated measures or by paired Student's *t*-test whenever appropriate. Significance for all tests was stated at the 0.05 probability level. Sensitivity, specificity, positive and negative predictive value rely on the standard definition and are reported with 95% confidence intervals (CI).

Results

Patient population

A total of 61 patients were included in the study. Mean age was 61 years (range, 43 to 77 years), and 49 were men. All patients were symptomatic, 57 had angina pectoris (29 in NYHA class II, 28 in NYHA class III) and 29 had dyspnea on effort (26 in NYHA class II, 3 in NYHA class III). Fifty-nine patients had a history of myocardial infarction (median of 24 months before study, range 4 to 210 months). The mean number of significantly stenosed coronary arteries was 2.7 ±

Table 1 Baseline characteristics of the entire study population, according to the LVEF (>35% versus ≤35%)

	LVEF >35% n = 22	LVEF ≤35% n = 39
Gender (M/F)	16 / 6	33 / 6
Age (yr) (mean ± SD)	61 ± 8	60 ± 9
Hypertension (%)	10 (45)	9 (23)
Diabetes Mellitus (%)	4 (18)	7 (18)
Previous CABG (%)	3 (14)	3 (8)
Old myocardial infarction	21	38
Q / non-Q wave	14 / 7	33 / 5
Angina pectoris (%)	20 (91)	37 (95)
Effort dyspnea (%)	5 (23)	24 (62)
Coronary arteriography	22	39
3 vessel disease (%)	14 (64)	29 (74)
2 vessel disease (%)	7 (32)	9 (23)
1 vessel disease (%)	1 (5)	1 (3)
LVEF (%) (mean ± SD)	41 ± 4	28 ± 5

CABG: coronary artery bypass grafting, LVEF: left ventricular ejection fraction.

0.5 and the mean LVEF was 33% (range, 17% to 49%). The baseline characteristics of the study group stratified into 2 groups according to LVEF (>35% versus ≤35%) are summarized in Table 1.

Baseline characteristics

Of a total of 976 myocardial segments, 19 were not adequately visualized by echocardiography whereas 28 were not revascularized. Therefore 929 segments were available for serial analysis. Abnormal resting wall motion was seen in 537

(58%) segments. Mild hypokinesis was observed in 240 segments, 82 segments were severely hypokinetic, 205 were akinetic and 10 were dyskinetic. Myocardial ischemia was demonstrated in 343/929 (37%) segments: in 100 normally contracting, 159 mildly hypokinetic, 53 severely hypokinetic and in 31 akinetic segments.

Outcome after uncomplicated revascularization

Three months after revascularization, only 3 patients had angina pectoris and 13 had dyspnea on effort (all in NYHA class II). Inducible myocardial ischemia decreased significantly after surgery from 343 to 20 segments ($p < 0.0001$; ≥ 2 segments in 5 patients). At late follow-up (median 14 months, range 11 - 19) 2 patients suffered from angina pectoris and 14 had dyspnea on effort (all in NYHA class II).

At 3 months, 136 of the 537 (25%) dyssynergic and revascularized segments showed improved wall motion at rest. Recovery was observed in 67 of 240 mildly hypokinetic, 35 of 82 severely hypokinetic, 32 of 205 akinetic and 2 of 10 dyskinetic segments. At late follow-up an additional 33 segments (25 mildly hypokinetic, 4 severely hypokinetic and 4 akinetic segments) showed improvement in contractile function, resulting in a total of 169 (31%) segments which showed recovery of contractile function late after revascularization. Furthermore, 8 severely hypo- or akinetic segments, already improvers at 3 months, showed further improvement at late follow-up. Deterioration of resting wall motion was noted in 8 of the 28 non-revascularized dyssynergic segments, in 35 of the 537 (7%) revascularized dyssynergic segments at 3 months and in 47 of the 537 (9%) at late follow-up. Of these 47 segments, 29 were ischemic during dobutamine infusion before revascularization.

At 3 months 12 patients showed significant improvement in LVEF. At late follow-up, an additional 7 patients improved, resulting in a total of 19 improvers. Thirteen of these patients had a preoperative LVEF $\leq 35\%$. Figure 1 shows the time course of recovery in global left ventricular function in the 19 improvers. The LVEF increased from 32 $\pm$ 8% to 37 $\pm$ 12% at 3 months to 42 $\pm$ 9% at late follow-up ($p < 0.0001$).

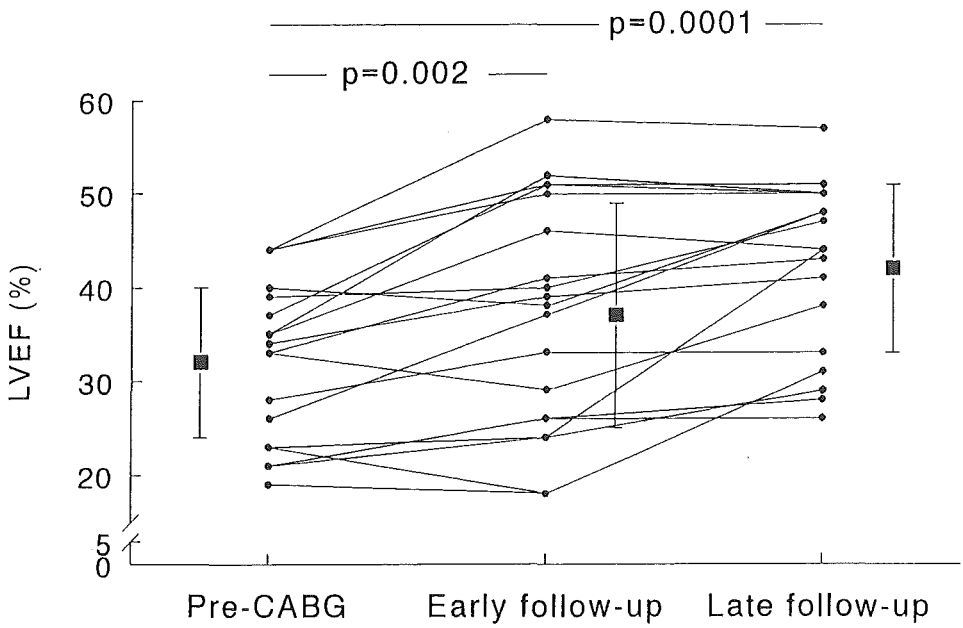

Figure 1 Graph showing the time course of recovery in left ventricular ejection fraction (LVEF) after coronary artery bypass surgery (CABG) in the 19 patients who significantly improved at late follow-up. The mean LVEF increased from 32 ± 8% to 37 ± 12% at 3 months to 42 ± 9% at late follow-up ($p < 0.0001$).

Dobutamine stress echocardiography

No serious complications occurred during the test. Heart rate increased from 71 ± 13 at rest to 136 ± 14 beats/min at peak stress ($p < 0.0001$). Systolic blood pressure did not change significantly (127 ± 18 mmHg at rest to 125 ± 22 mmHg at peak stress). Heart rate but not systolic blood pressure increased significantly at low-dose dobutamine compared to baseline values (83 ± 19 beats/min and 126 ± 20 mm Hg respectively). Five patients were on ß-blockers during the preoperative dobutamine stress test. Forty-five patients received the maximal 40 μg/kg/min dose of dobutamine. Atropine was administered in 28 patients. Angina occurred in 40 (66%) patients, and ST-deviation in 40 (66%) patients. The reasons for termination of the test were angina (n = 39), reaching >85% maximal heart

rate (n = 20) with or without signs of myocardial ischemia, wall motion abnormalities (n = 1) and hypotension (n = 1).

Of a total of 537 segments with abnormal wall motion that were successfully revascularized, 186 (35%) segments exhibited a biphasic response, 58 (11%) demonstrated sustained improvement, 68 (12%) showed worsening (without improvement) and 225 (42%) showed no change in regional wall motion during dobutamine challenge.

Functional recovery versus response during dobutamine echocardiography
Analysis by segments

The different types of response to dobutamine infusion in relation to the functional outcome of all dyssynergic segments after revascularization at 3 months and at late follow-up is depicted in Figure 2. At 3 months, 118/186 (63%) segments with a biphasic response improved in wall motion, whereas the other 3 patterns were not predictive for functional recovery. At late follow-up, 140/186 (75%) segments with a biphasic response showed improvement of wall motion. Also segments with sustained improvement showed a trend to recover at late follow-up (22%). Assuming a biphasic response as indicative for recovery and the other 3 predefined patterns as indicative for no recovery, the sensitivity, specificity, positive - and negative predictive values for functional recovery are 87% (CI, 81% to 93%), 83% (CI, 79% to 87), 63% (CI, 56% to 70%) and 95% (CI, 93% to 97%) at 3 months follow-up, and at late follow-up 83% (CI, 77% to 89%), 88% (CI, 85% to 91%), 75% (CI, 69% to 81%) and 92% (CI, 89% to 95%) respectively.

Figure 3 shows the influence of severity of segmental LV dysfunction at baseline on the predictive value of dobutamine echocardiography and the timing of the follow-up study. It clearly demonstrates a much less accurate prediction for functional recovery in mildly hypokinetic segments compared to severely hypokinetic/akinetic segments. Additionally it shows that the positive predictive value of both mildly hypokinetic- and severely hypokinetic/akinetic segments improves when late follow-up is considered (H: 67% (CI, 59% to 75%) versus 53% (CI, 44% to 62%) and SH/AK: 90% (CI, 83% to 97%) versus 81% (CI, 72% to 90%).

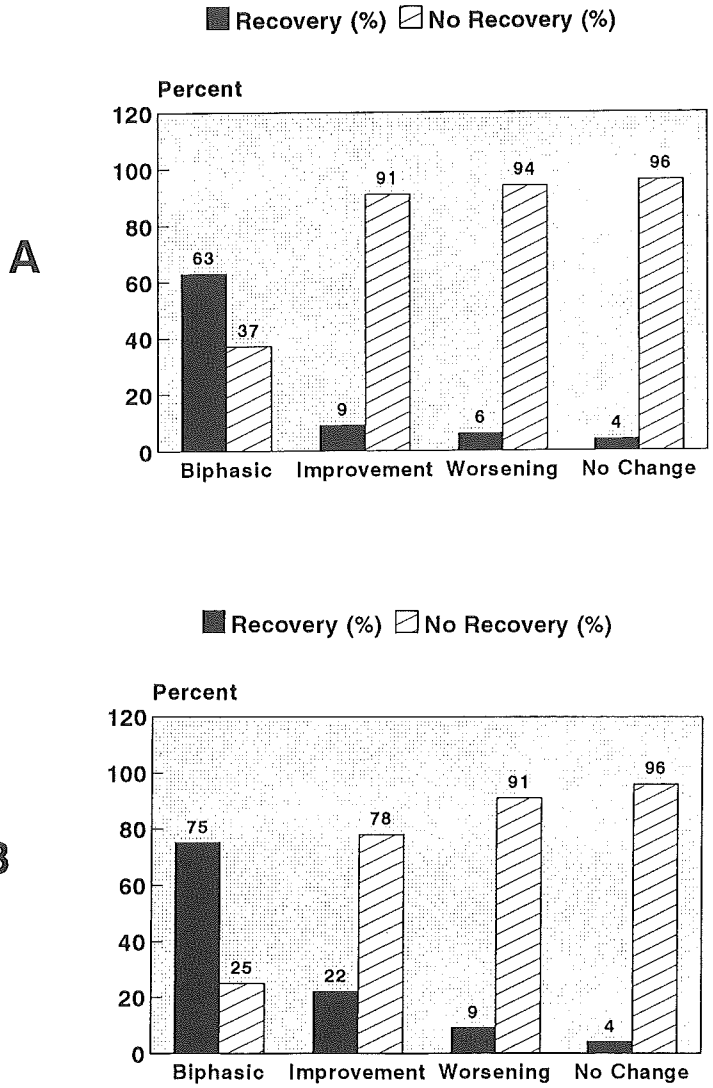

Figure 2 Bar graph demonstrating prediction of recovery of regional ventricular function 3 months (A) and 14 months (B) after surgical revascularization related to the preoperative different types of responsiveness to dobutamine infusion.

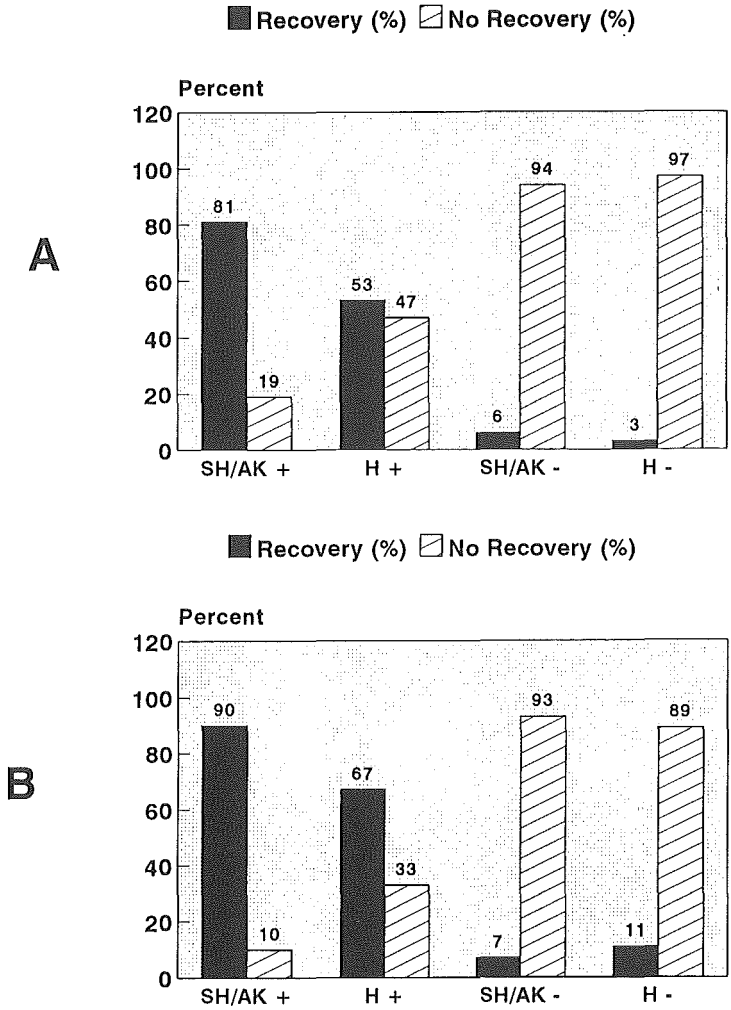

Figure 3 Bar graph demonstrating prediction of recovery of regional ventricular function 3 months (A) and 14 months (B) after surgical revascularization related to the preoperative degree of wall motion abnormality and different type of responsiveness to dobutamine infusion. SH/AK +: severely hypokinetic or akinetic segments with a biphasic response, SH/AK -: severely hypokinetic or akinetic segments without a biphasic response including sustained improvement, H +: mildly hypokinetic segments with a biphasic response, H -: mildly hypokinetic segments without a biphasic response.

Table 2 Diagnostic accuracy with 95% confidence intervals at 3 months and at late follow-up of dobutamine responsiveness in hypokinetic- and severely hypokinetic/akinetic segments for the prediction of postoperative improvement of regional wall motion abnormalities

	dyssynergy	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)
3 months	SH/AK	80	94	81	94
	95% CI	71 - 89	91 - 97	72 - 90	91 - 97
	H	94	68	53	97
	95% CI	88 - 100	61 - 75	44 - 62	94 - 100
Late	SH/AK	79	97	90	93
	95% CI	70 - 88	95 - 99	83 - 97	90 - 96
	H	86	74	67	89
	95% CI	79 - 93	67 - 81	59 - 75	84 - 94

SH/AK: severely hypokinetic or akinetic segments, CI: confidence interval, H: mildly hypokinetic segments, PPV: positive predictive value, NPV: negative predictive value.

Table 2 shows the diagnostic accuracy with 95% CI at 3 months and late follow-up of dobutamine responsiveness in mildly hypokinetic and severely hypokinetic/akinetic segments demonstrating significant better specificity and positive predictive value in segments with the most severe wall mation abnormalities at baseline.

Analysis by patients

To give more insight into the relation between the number of segments showing a biphasic response per patient and the magnitude of change in LVEF at late follow-up, linear regression analysis was performed (Figure 4). It shows that most (17/25) patients with ≥ 4 jeopardized but viable segments improve their global LV function after revascularization ($r = 0.61$). The sensitivity and specificity for the detection of functional recovery of global LV function ($\geq 5\%$ increase of LVEF) at late follow-up were determined in all patients and in 2 subsets with

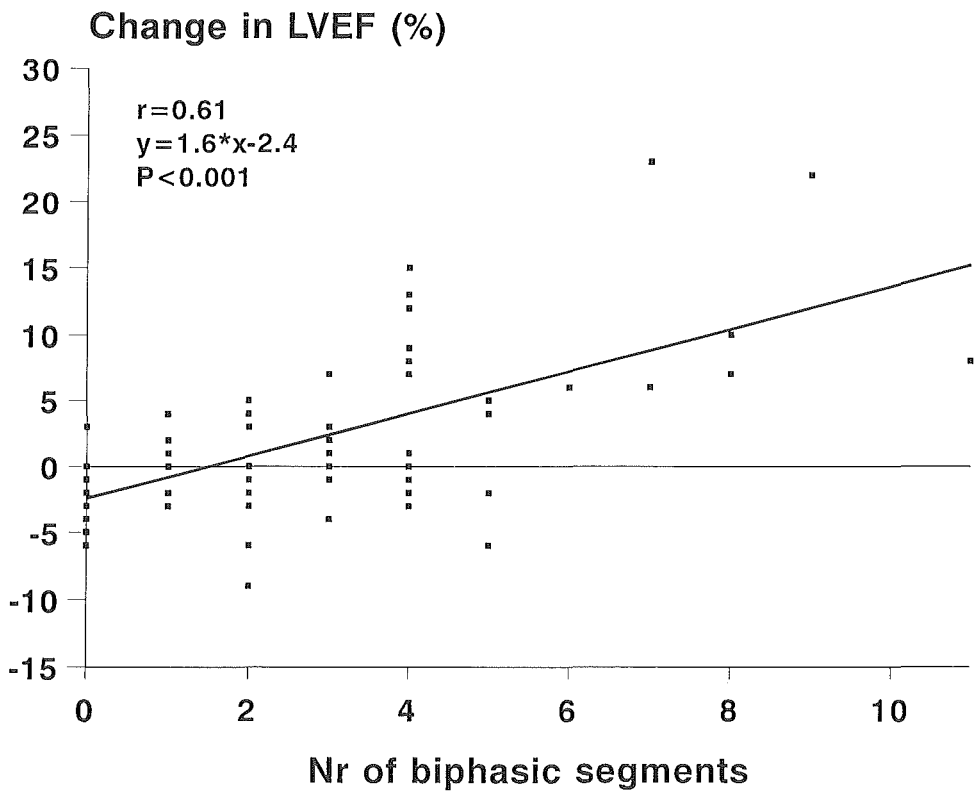

Figure 4 Postoperative change in left ventricular ejection fraction (LVEF) at late follow-up related to the number of segments with a biphasic response in 61 patients.

either rather preserved or diminished LV function (Table 3). In patients with a LVEF of $\leq 35\%$ the diagnostic accuracy of the test seems similar.

Discussion

The accurate prediction of improvement of contractile function of chronically dysfunctional myocardium after successful revascularization is crucial for the proper selection of therapeutic stategies. Few studies have addressed the time course of recovery of LV function.[26,27] Insight into the time course of recovery

Table 3 Sensitivity and specificity of dobutamine echocardiography to predict recovery of global left ventricular function at late follow-up

	sensitivity (%)	specificity (%)
All patients (n = 61)	89 (17/19)	81 (34/42)
Patients with LVEF ≤35% (n = 39)	92 (12/13)	81 (21/26)
Patients with LVEF >35% (n = 22)	83 (5/6)	81 (13/16)

LVEF: left ventricular ejection fraction.

may further support clinical decision making. In this prospective study we have tried to evaluate several potential factors which may influence the diagnostic accuracy of dobutamine stress echocardiography in predicting the effects of revascularization on contractile function in patients with chronic ischemic LV dysfunction.

The main findings are as follows.

1) Global LV function significantly improves in one third of patients after revascularization, even in the subset with a LVEF ≤35%.

2) Serial post-operative follow-up studies demonstrate incomplete recovery at 3 months. Beyond 3 months, additional improvement of contractile function occurred both on a segmental basis (31% versus 25%) and in global LV function (31% versus 22%).

3) A biphasic response to dobutamine is predictive for post-operative improvement in regional contractile function (75% at late follow-up). The other patterns of dobutamine responsiveness are highly predictive for non-recovery (92% at late follow-up). This results in a sensitivity of 83% and a specificity of 88% at late follow-up.

4) The diagnostic accuracy of dobutamine responsiveness is best in segments with the most severe wall motion abnormalities at baseline.

5) Dobutamine stress echocardiography in the aforementioned clinical setting has a sensitivity of 89% and a specificity of 81% to predict functional recovery of global LV function on a patient basis.

All previous studies with dobutamine echocardiography have used echocardiography to assess improvement of wall motion, without an independent technique to verify these data.[12-20] In the present study we have circumvented this problem using serial radionuclide ventriculographic studies for the assessment of changes in global LV function. Our study is also unique in reporting the effects of sequential follow-up studies on the diagnostic accuracy of the test for post-revascularization improvement of both regional and global LV function. It provides more insight into the clinical relevance of the test since it includes analysis on an individual patient basis. In line with previous studies, a patient was expected to improve in global LV function at late follow-up when at least 4 abnormal contracting segments at baseline (25% of the myocardium) demonstrated a biphasic response to dobutamine. Furthermore this study adds to the accumulating evidence that high dose dobtamine stress testing, even with atropine on top, can be performed safely without serious complications also in patients with poor LV function.[28]

Biphasic response

Several studies, experimental or clinical using a head to head comparison between dobutamine stress echocardiography and myocardial perfusion scintigraphy, describe a relation between a biphasic response to dobutamine and myocardial scintigraphic ischemia.[29-31] This can be explained by the presence of viable tissue in a segment subtended by a stenotic coronary artery, exhibiting a contractile response to low-dose dobutamine and ischemia at high dose dobutamine provoked by the increased rate pressure product and flow maldistribution. An alternative explanation has been proposed by Schultz and coworkers.[32,33] In a swine model of short-term hibernation, using a continuous intracoronary dobutamine infusion, they showed that both myocardial ischemia and depletion of high-energy phosphates explain the biphasic response. It remains unclear whether the increasing dosage of dobutamine or the duration of dobutamine infusion is responsible for the late decrease in myocardial thickening in segments exhibiting a biphasic response.

In the present study, the majority of segments demonstrating such a biphasic response recovered in contractile function after revascularization. These findings are in line with data reported by Afridi et al.[16] It is likely that after successful revascularization high-energy phosphate stores are ensured through adequate myocardial perfusion at rest and at stress. Under these circumstances dyssynergic myocardium may recover frequently.

Other types of dobutamine responsiveness

In segments demonstrating a sustained improvement during dobutamine, it is likely that enough high-energy phosphates are present to maintain enhanced contractility until the final stage of the test. Only 22% of the segments with sustained improvement showed recovery after revascularization. Since these segments are unlikely to be exposed to repeated ischemic insults preoperatively, they may recover less frequently after revascularization. An alternative explanation for the low recovery rate of segments with sustained improvement may be the coexistence of coronary artery disease with cardiomyopathy. Segments with direct worsening in wall motion during dobutamine challenge rarely improved after revascularization. It is conceivable that these segments contain a mixture of scar tissue and normal myocardium becoming ischemic during dobutamine infusion. Although Afridi et al[16] reported a higher recovery rate of these segments (35%), one should bear in mind that in absolute terms this represents only 6 segments. Finally the lack of change in wall thickening during dobutamine infusion is a very specific marker for the prediction of lack of functional improvement after surgical revascularization. This echocardiographic pattern of non-responding to dobutamine therefore is in agreement with the diagnosis of scar with no clinical relevant amount of residual viable myocardium. This observation is quite relevant, since it suggests that, in patients with chronic advanced ischemic LV dysfunction, further tests for the assessment of potential reversibility of dysfunction in segments with this specific echocardiographic pattern are redundant.

Mildly versus severely dyssynergic segments

Previous studies with low-dose dobutamine echocardiography have concentrated on the prediction of regional recovery after revascularization. They

show sensitivities ranging from 71% to 97% (weighted mean 85%) and specificities ranging from 63% to 95% (weighted mean 89%).[12,14-20] Our results add to the accumulating evidence that the test is an accurate method for the evaluation of myocardial viability in patients with chronic dysfunctional myocardium due to coronary artery disease. In our study, both specificity and positive predictive value improved when only severely dyssynergic segments were evaluated, similar to previous studies.[14,15,18] Mildly hypokinetic segments are likely to contain normal myocardium, subendocardial scar and/or viable but dysfunctional myocardium. If relatively little viable tissue is present, dobutamine challenge may stimulate normal myocardium to a hyperkinetic response simulating a positive test for viability. If on the other hand a substantial amount of viable myocardium is present, a similar test result may appear. But only in the latter example one expects functional recovery to occur after revascularization. False positive tests occur less often in severe dyskinesis since the presence of normal myocardial tissue is minimal in segments with severe contractile dysfunction.

Prediction of improvement in global LV function

In this study we showed that patients with ≥ 4 jeopardized but viable segments (25% of the myocardium) are likely to improve global LV function. The data confirm earlier studies[17,34-38] employing different techniques to assess myocardial viability, and indicate that a substantial amount of viable but jeopardized myocardium needs to be present to result in improved global LV function. This observation implies, if confirmed in larger series, that dobutamine stress echocardiography is a reliable technique to predict functional outcome after revascularization. An accurate prediction is of paramount importance for the selection of the most appropriate treatment in individual patients with chronic ischemic poor LV function, since LVEF is an important predictor for survival.

Timing of functional recovery

The optimal timing for the assessment of functional recovery after revascularization is essential for the correct interpretation of the diagnostic accuracy of a given test. Currently, functional follow-up studies in chronic coronary artery disease are performed frequently within 3 months after the

revascularization procedure.[14-20,38] However, in individual patients all types of reversible and irreversible contractile dysfunction may coexist and in them it is impossible to distinguish repetitive myocardial stunning from hibernation. In stunned myocardium recovery of function may occur within days or weeks. Given the severity of structural changes observed in hibernating myocardium,[21,22] it is likely that under these conditions recovery of function after revascularization is delayed. Therefore, complete recovery of contractile function should not be expected before 4 to 8 months after revascularization in patients with chronic coronary artery disease. Our data support these concepts since 7 of the 19 improvers at late follow-up did not show improvement of global LV function at 3 months. Such delayed recovery after CABG has been described earlier[26,27,39] and underlines the importance of late follow-up studies after revascularization procedures in this clinical setting.

Limitations of the study

Incomplete revascularization may prohibit viable segments to recover, thereby underestimating the diagnostic accuracy of a diagnostic technique. Since we did not perform repeated angiography after surgery to assess graft patency, we are not informed about the successfulness of coronary revascularization. However repeated dobutamine stress echocardiographic studies performed 3 months after CABG revealed a decrease in inducible myocardial ischemia from 343 to 20 segments. This study was performed in an experienced center dealing with patients with LV dysfunction and thus it represents daily clinical practice.

Since we did not study patients at 6 months, we are not informed about the completeness of recovery at 6 months. Therefore we cannot comment about this issue regarding the optimal timing of follow-up studies for the detection of complete recovery of contractile function after CABG in the aforementioned clinical setting. Detailed and larger studies are needed to answer this question.

Regional wall thickness has not been measured. Normal end-diastolic thickness has been described as marker of myocardial viability and a predictor of recovery after revascularization.[40,41] On the other hand, dyssynergic segments with severely reduced thickness rarely show improved contractile function after revascularization. Further studies are needed to answer the question what the

additional value is of dobutamine challenge on top of wall thickness measurements.

Patients with poor LV function may potentially benefit most from myocardial viability studies given the condition that viability leads to improvement of global LV function. Since only a small number of patients with poor LV function were studied we cannot draw firm conclusions about the diagnostic accuracy of dobutamine stress echocardiography for the prediction of functional recovery in these patients.

Conclusions

Serial post-operative follow-up studies demonstrate substantial incomplete recovery of contractile function at 3 months. Dobutamine stress echocardiography is an useful method to predict improvement of regional and global LV function after CABG. Its diagnostic accuracy depends on combining low and high doses of dobutamine infusion, severity of dyssynergy and the timing of evaluation. This study contributes to the increasing clinical experience with dobutamine stress echocardiography in patients with stable ischemic LV dysfunction.

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Chapter 11

Summary and Future Perspectives

Summary

Detection of myocardial viability has gained importance in clinical cardiology. The increasing number of patients with left ventricular (LV) systolic dysfunction due to ischemic injury and the awareness of the potential reversibility of LV systolic dysfunction after revascularization has led to a search for accurate and readily available diagnostic methods to detect residual viable myocardium. Myocardial perfusion imaging may detect viable myocardium, since tracer uptake requires adequate microvascular perfusion, cellular integrity and metabolic function. Recruitment of contractile reserve in hypocontractile myocardial segments by using inotropic stimuli also reflects residual viability but represents a different cellular mechanism than perfusion. Indeed, the concept of metabolically viable myocardium must be distinguished from the ability to recover mechanical myocardial function. Dobutamine stress echocardiography may serve as an alternative for myocardial perfusion and metabolic imaging techniques for the recruitment of myocardial residual function. In this thesis, several different diagnostic techniques are evaluated for their ability to identify patients who are likely to improve resting LV function after myocardial infarction or after revascularization procedures.

In Chapter 2, the value of resting sestamibi imaging to distinguish viable myocardium from scar tissue and to predict functional recovery has been discussed. Sestamibi is a technetium-99m labeled myocardial perfusion agent. The uptake of sestamibi is dependent upon cell membrane integrity and mitochondrial function. The results of all comparative studies between sestamibi imaging and other viability tracers such as thallium-201 (^{201}Tl) or ^{18}F-FDG using positron emission tomography suggest that sestamibi underestimates the presence of severely hypoperfused but still viable myocardium in patients with chronic coronary artery disease. However, recent data suggest that the differences between ^{201}Tl and sestamibi are smaller when nitrates are administered in combination with quantitative analysis and when late imaging is used. Despite its lower sensitivity for detecting viable myocardium, sestamibi tracer uptake may allow for adequate prediction of functional recovery after successful revascularization. Indeed, failing to detect limited amounts of viable myocardium has no major impact on the diagnostic accuracy in predicting the outcome of revascularization. Only a small number of limited studies have

addressed the role of sestamibi in predicting functional recovery after revascularization. Therefore, the exact value of sestamibi imaging has still to be defined.

In Chapter 3 we reported the results of a study addressing the concordance between the two currently most advocated ^{201}Tl imaging protocols, post-stress ^{201}Tl redistribution-reinjection and rest-redistribution ^{201}Tl SPECT, for the detection of myocardial viability in patients with chronic coronary artery disease and depressed LV function. An excellent agreement between the two protocols was found, even after omission of the post-stress redistribution scan. The use of a semi-quantitative analysis of the SPECT results was crucial to reach such high concordance. The high level of agreement sustained when the analysis was limited to dyscontractile myocardial segments. These results justify the use of dobutamine stress-reinjection ^{201}Tl SPECT without the acquisition of redistribution images, in detecting residual myocardial viability in patients with chronic coronary artery disease.

The safety and feasibility profile of high dose dobutamine-atropine stress echocardiography in 318 patients with ischemic LV dysfunction is reported in Chapter 4. In our study, no serious complications (myocardial infarction, ventricular fibrillation or death) occurred. In patients with a LV ejection fraction of 25% or less, there was a higher incidence of significant tachyarrhythmias (14% versus 5%), but the feasibility of the test remained high. Multivariate analysis indicated that a history of tachyarrhythmias was the only predictor of stress-induced arrhythmias. Therefore, advanced LV dysfunction on itself does not represent a risk factor for serious complications or adverse effects during dobutamine-atropine stress testing.

The second part of this thesis represents the results of studies aimed at evaluating various diagnostic methods for the identification of dyscontractile myocardium likely to improve mechanical function.

In Chapter 5 the prevalence of spontaneous improvement of regional LV dysfunction in 57 unselected patients after a first uncomplicated acute myocardial infarction (thrombolysis, n = 27) was assessed. Approximately one fourth of the dyscontractile segments showed functional recovery at 3 month follow-up. Spontaneous recovery occurred more frequently in hypokinetic than in akinetic segments (35% versus 19%). It was demonstrated that low-dose dobutamine stress

echocardiography provides specific information for predicting lack of improvement at follow-up in these patients. Also, the test has a high sensitivity for predicting functional improvement in hypokinetic segments, but was not useful in identifying akinetic segments which improve spontaneously.

Evaluation of ECG changes during a low-dose dobutamine stress test may also be helpful for identifying dyssynergic but still viable myocardium in patients after a recent Q-wave myocardial infarction (Chapter 6). In a group of 90 postinfarction patients with negative T waves in ≥ 2 infarct-related ECG leads, we tested the hypothesis that T-wave normalization during low-dose dobutamine infusion represents residual viable myocardium. A good agreement was found between low-dose dobutamine induced T-wave changes and wall motion changes. Furthermore, the sensitivity of low-dose dobutamine stress echocardiography for predicting late spontaneous recovery of segmental wall motion at 3 month follow-up increased, without loss of specificity, when the T-wave changes on the ECG were added to the analysis. Thus T-wave normalization during low-dose dobutamine stress testing provides additional information to identify viable myocardium after acute myocardial infarction.

In patients with stable chronic coronary artery disease accepted for myocardial revascularization, we have performed three studies describing the direct comparison of two tests for the prediction of functional outcome of resting regional and, or global LV function at 3 month follow-up (Chapters 7-9). In these patients approximately 30% of the dyscontractile segments showed functional recovery at 3 month follow-up. Most patients in whom residual viability in more than 25% of the LV was demonstrated, showed post-operative improvement of global LV function. Similarly to the spontaneous recovery observed after acute myocardial infarction, recovery after revascularization occurred more frequently in hypokinetic than in akinetic segments.

In Chapter 7 we report our study on low-dose dobutamine stress echocardiography which was compared with dobutamine stress-reinjection ^{201}Tl SPECT in 38 patients in predicting functional recovery of 170 severely hypokinetic or akinetic segments. All patients had severe LV dysfunction. ^{201}Tl SPECT demonstrated residual viability more frequently than low-dose dobutamine stress echocardiography (61% versus 19%). However, post-operative recovery was grossly overestimated

by ^{201}Tl SPECT resulting in a modest specificity of 48% as compared the 96% specificity of low-dose dobutamine stress echocardiography. In contrast to the results described in Chapter 5, the responsiveness of severely dysfunctional segments to low-dose dobutamine stress was also a sensitive predictor of post-operative recovery, similar to ^{201}Tl SPECT. Thus, ^{201}Tl SPECT appears to be less useful than low-dose dobutamine stress echocardiography to predict the post-operative improvement of regional wall motion in patients with severe LV dysfunction. The data also suggest that the cellular mechanism responsible for a positive inotropic response to dobutamine stimulation requires a higher degree of myocyte functional integrity than the metabolic mechanism responsible for ^{201}Tl uptake. For recovery of contractile function a "critical mass" of viable myocytes must be available.

Since it is feasible to image myocardial FDG uptake with a conventional gamma camera using 511 keV collimators, we have evaluated the use of FDG SPECT for its prediction of functional recovery in 55 patients prior to revascularization and compared this technique with rest-redistribution ^{201}Tl SPECT in a subgroup of 24 patients (Chapter 8). Dysfunctional segments with a resting perfusion defect and increased FDG uptake, a perfusion-metabolism mismatch, had a significant functional recovery. Considering both normal perfusion and a mismatch as indicative for recovery, FDG SPECT reached a sensitivity of 85% and a specificity of 75% to predict functional recovery. In hypokinetic segments the specificity was lower in comparison to akinetic segments. Global LV function improved significantly in patients with $\geq$3 viable (of the 13) segments on FDG SPECT. These results are similar to those reported using positron emission tomography and suggest that FDG SPECT, in spite of its lower spatial resolution, can be helpful in the clinical management of patients with chronic ischemic LV dysfunction. In direct comparison FDG SPECT showed a better specificity as compared to rest-redistribution ^{201}Tl SPECT (77% versus 57%). Stepwise logistic regression analysis of the FDG and ^{201}Tl rest-redistribution data showed that a perfusion-metabolism mismatch was the best predictor of functional recovery. All other parameters did not contribute independently. Thus FDG SPECT seems superior to rest-redistribution ^{201}Tl SPECT in the identification of patients in whom regional and global LV function can improve after revascularization.

In Chapter 9 FDG SPECT was compared with low-dose dobutamine stress echocardiography. Both techniques demonstrate similar high diagnostic accuracies in detecting post-operative improvement of regional and global LV function. However in mildly hypokinetic segments both techniques, but especially low-dose dobutamine stress echocardiography, overestimate the probability of post-operative recovery (specificity 45% versus 74% for SPECT). Since in clinical practice the issue of myocardial viability is mainly relevant in severe contraction abnormalities, this should not be considered an important limitation.

In Chapter 10 we evaluated the time course of functional improvement after coronary artery bypass graft surgery (CABG). The follow-up period was 1 year. We further explored the value of dobutamine stress echocardiography by combining low- and high-dose dobutamine. Of the 61 patients, global LV function improved in 12 at 3 months and in a total of 19 at late follow-up. A biphasic response to dobutamine, defined as contractile improvement at low-dose and worsening at peak stress, was predictive for segmental functional recovery in 63% at 3 months and in 75% at late follow-up. Other responses were highly predictive for non-recovery. Thus the combination of dysfunctioning myocardium which shows improvement after dobutamine stimulation at low dose and inducible ischemia more likely predicts recovery after revascularization than viable myocardium which is not in jeopardy. Again, similar to our findings in Chapter 9, the positive predictive value was dependent on the severity of the contraction abnormality at rest. The highest accuracy was reached in akinetic segments. The test was also accurate in predicting improvement of global LV function at late follow-up. In the presence of ≥ 4 jeopardized segments prior to surgery, ejection fraction improved with at least 5 points in 68% of the patients. Thus, serial post-operative follow-up studies demonstrate incomplete recovery of regional and global contractile function at 3 months. Furthermore, the diagnostic accuracy of dobutamine stress echocardiography to predict recovery seems to depend on combining low and high dose dobutamine stimulation, severity of dyssynergy at baseline and the timing of evaluation.

Conclusions and future perspectives

In patients with chronic ischemic LV dysfunction, both dobutamine stress

echocardiography and FDG SPECT are useful methods to detect dysfunctional but viable myocardium likely to recover after adequate revascularization. Viable myocardium which is in jeopardy seems more likely to recover than viable myocardium which is not in jeopardy. Therefore both techniques, by detecting either a biphasic contractile response or a perfusion-metabolism mismatch, have high diagnostic accuracies. The exact value of scintigraphic perfusion techniques remains unclear. It is likely that the traditional criteria of ^{201}Tl SPECT used for the identification of myocardial viability are not optimal for the prediction of functional recovery. Furthermore the implications of an extended follow-up of 1 year on the diagnostic accuracy of SPECT has not been addressed and several other questions remain to be answered.

The studies described in this thesis concentrated on the potential of viable myocardium to improve resting systolic LV function. Other potential aspects of viable myocardium may have clinical importance such as the prevention of infarct expansion, preservation of contractile reserve and, perhaps reversing remodeling. This may improve the functional status of the patient, increase exercise capacity (quality of life) and delay the development of heart failure. At present there are no data available concerning these topics. Preliminary data using positron emission tomography indicate that revascularization of areas with perfusion-metabolism mismatch may favourably influence prognosis. Furthermore, larger studies are needed in patients with severely impaired LV function to determine the value of the detection of viable but jeopardized myocardium to predict recovery of global LV function after successful revascularization. There are indications that both contractile reserve and baseline end-diastolic volume (as a sign of severity of LV remodeling) are independent predictors of post-operative improvement of global LV function.

Samenvatting

Samenvatting

De opsporing van vitaal myocard wordt steeds belangrijker in de dagelijkse cardiologische praktijk. Niet alleen neemt het aantal patienten toe met een gestoorde linker ventrikel (LV) funktie door ischemische schade, tevens groeit het besef dat de LV funktie kan herstellen na revascularisatie. Dit heeft geleid tot het ontwikkelen van goede, relatief eenvoudige diagnostische methoden om vitaal myocard op te sporen.

Het afbeelden van myocardiale perfusie levert hieromtrent informatie op, daar tracer opname afhankelijk is van de mate van microvasculaire perfusie, van cellulaire integriteit en metabole funktie. Hoewel het aantonen van contractiele reserve van dysfunctioneel myocard door middel van een inotrope stimulus ook een uiting is van vitaliteit, is er hierbij sprake van een ander cellulair mechanisme. Het concept van metabool levend myocard dient te worden onderscheiden van het vermogen tot herstel van de LV funktie. Dobutamine stress echocardiografie kan een alternatief zijn voor afbeeldingstechnieken van myocardiale perfusie en metabolisme om de mogelijkheden tot herstel van de LV funktie te voorspellen. In dit proefschrift zullen verschillende diagnostische methoden worden onderzocht op het vermogen om patienten te identificeren bij wie de LV funktie zal gaan herstellen, zowel spontaan na een acuut hartinfarct als na een revascularisatie procedure.

In hoofdstuk 2 wordt de waarde van sestamibi scintigrafie besproken. Sestamibi is een aan technetium gekoppeld radiofarmacon. De myocardiale opname van sestamibi is afhankelijk van de integriteit van de celmembraan en van de mitochondriale funktie. Vergelijkende studies tussen sestamibi scintigrafie en thallium-201 (^{201}Tl) scintigrafie of ^{18}F-FDG positron emissie tomografie wijzen erop, dat sestamibi de aanwezigheid van dysfunctionerend maar nog vitaal myocard onderschat bij patienten met chronisch coronairlijden. De verschillen tussen ^{201}Tl en sestamibi blijven echter beperkt als een voorbehandeling met nitraten in combinatie met kwantitatieve beeldanalyse plaats vindt, alsmede wanneer late beeldacquisitie wordt toegepast. Ondanks de wat lagere sensitiviteit voor het opsporen van vitaal myocard kan sestamibi scintigrafie theoretisch nog steeds het mogelijke herstel van pompfunktie na revascularisatie accuraat voorspellen. Immers, de mate van onderschatting en niet de onderschatting zelve bepaald de

nauwkeurigheid in het voorspellen hiervan. De waarde van sestamibi scintigrafie voor het voorspellen van het herstel van pompfunktie na revascularisatie blijft vooralsnog onduidelijk, daar tot op heden slechts een beperkt aantal kleine onderzoeken hiernaar zijn verricht.

In hoofdstuk 3 wordt een vergelijkend onderzoek besproken naar de waarde van 2 verschillende ^{201}Tl protocollen, te weten dobutamine stress-redistributie-reinjectie en rust-redistributie, voor wat betreft de detectie van myocardiale vitaliteit. Zelfs zonder gebruik te maken van de post-stress redistributie scan werd een uitstekende overeenkomst tussen beide protocollen gevonden. Om tot een dergelijke goede overeenkomst te komen, was het toepassen van semi-kwantitatieve gegevens verwerking essentieel. Aldus is het dobutamine stress-reinjectie ^{201}Tl SPECT protocol goed bruikbaar voor vitaliteitsonderzoek bij patienten met chronisch coronairlijden.

De veiligheids- en haalbaarheidsaspecten van dobutamine-atropine stress echocardiografie bij 318 patienten met ischemisch bepaalde LV dysfunktie worden belicht in Hoofdstuk 4. Bij dit onderzoek deden zich geen ernstige complicaties voor (acuut myocardinfarkt, ventrikelfibrilleren of overlijden). Patienten met een slechte LV funktie (ejectie fraktie 25% of minder) kregen wel vaker tachyaritmieën tijdens de test (14% versus 5%). Bij multivariate analyse bleek dat alleen een anamnese van tachyaritmieën een voorspellende waarde had voor het optreden van aritmieën tijdens de stress test. Dus zelfs in patienten met een slechte LV funktie kan de dobutamine-atropine stress test veilig en zonder al te veel problemen worden uitgevoerd.

Het tweede deel van dit proefschrift beschrijft de resultaten van verschillende onderzoeken naar de evaluatie van een aantal diagnostische methoden om herstel van LV funktie te voorspellen.

In hoofdstuk 5 wordt spontaan herstel beschreven van regionale LV dysfunktie in 57 ongeselecteerde patienten na hun eerste acute hartinfarkt (27 van hen waren met thrombolyse behandeld). Ongeveer een kwart van de dysfunctionerende segmenten vertoonde herstel na 3 maanden. Het spontane herstel trad vaker in hypokinetische segmenten dan in akinetische segmenten op (35% versus 19%). Dobutamine stress echocardiografie met behulp van een lage dosis

dobutamine (LDDE) gaf specifieke informatie over het voorspellen van de afwezigheid van herstel na 3 maanden. Alhoewel de sensitiviteit voor het voorspellen van herstel in hypokinetische segmenten hoog was, bleek de techniek niet bruikbaar voor het voorspellen van herstel in akinetische segmenten.

Hoofstuk 6 beschrijft de additionele waarde van ECG veranderingen tijdens LDDE voor het identificeren van vitaal myocard in patienten na een recent transmuraal myocardinfarct. In 90 postinfarct patienten met negatieve T-toppen op het ECG werd onderzocht, of T-top normalisatie tijdens dobutamine infusie een teken is van residuele myocardiale vitaliteit. Er werd een goede overeenkomst gevonden tussen het optreden van T-top normalisatie en het bestaan van contractiele reserve. De sensitiviteit van LDDE voor het voorspellen van spontaan herstel na 3 maanden, nam toe indien de ECG bevindingen werden toegevoegd aan de beoordeling van de echocardiografie.

In de hoofdstukken 7 t/m 9 worden 3 studies beschreven waarbij 2 methoden worden vergeleken voor het voorspellen van verbetering van regionale en globale LV funktie na revascularisatie. Het betreft ditmaal stabiele patienten met chronisch coronairlijden. Na 3 maanden bleek ongeveer 30% van de dysfunctionerende segmenten herstel te vertonen. De meeste patienten met meer dan 25% residuele vitaliteit van de linker ventrikel vertoonden een verbetering van de globale LV funktie. Het herstel na revascularisatie kwam vaker voor in hypokinetische segmenten dan in akinetische segmenten.

In hoofdstuk 7 wordt een studie beschreven, waarin bij 38 patienten LDDE werd vergeleken met dobutamine stress-reinjectie ^{201}Tl SPECT voor het voorspellen van herstel van 170 ernstig dysfunctionerende segmenten. Alle patienten hadden een sterk verminderde LV funktie. Residuele vitaliteit werd vaker aangetoond met ^{201}Tl SPECT in vergelijking met LDDE (61% versus 19%). Het postoperatieve herstel werd echter in hoge mate overschat door ^{201}Tl SPECT in vergelijking met LDDE (specificiteit 48% versus 96%). In tegenstelling tot de in hoofdstuk 5 beschreven resultaten, bleek de door dobutamine geïnduceerde contractiele reserve een goede voorspeller te zijn van herstel van ernstig dysfunktionerende segmenten en vergelijkbaar met ^{201}Tl SPECT. Derhalve lijkt ^{201}Tl SPECT minder bruikbaar te zijn dan LDDE voor het voorspellen van postoperatief herstel van regionale wandbeweging in patienten met een sterk verminderde LV funktie. Deze resultaten

suggereren, dat voor een positief inotrope respons een grotere mate van myocyt integriteit nodig is dan voor het verkrijgen van myocardiale ^{201}Tl opname. Voor het herstel van contractiliteit is een "kritisch" aantal vitale myocyten een conditio sine qua non.

In hoofdstuk 8 wordt de toepassing beschreven van FDG SPECT voor het voorspellen van funktioneel herstel van de LV funktie na revascularisatie. Aan dit onderzoek namen 55 patienten deel; bij 24 van hen werd tevens een rust-redistributie ^{201}Tl SPECT verricht. Door de ontwikkeling van 511 keV collimatoren is mogelijk geworden de opname van FDG af te beelden met een conventionele gamma camera. Dysfunktionerende segmenten met een perfusiedefect en relatief verhoogde FDG opname (perfusie-metabolisme mismatch) vertoonden in hoge mate funktioneel herstel. Indien zowel normale perfusie als een mismatch als aanwijzing voor herstel werd beschouwd, bleek met FDG SPECT een sensitiviteit van 85% en een specificiteit van 75% haalbaar. De specificiteit in hypokinetische segmenten was lager vergeleken met akinetische segmenten. In patienten met ≥ 3 (van de 13) vitale segmenten werd een significante verbetering van de globale LV funktie aangetoond. Deze resultaten komen overeen met de beschreven resultaten van positron emissie tomografie. Onze studie suggereert, dat FDG SPECT ondanks een lager onderscheidend vermogen, nuttig kan zijn bij de zorg voor patienten met een ischemische cardiomyopathie. Vergeleken met rust-redistributie ^{201}Tl SPECT bleek de specificiteit van FDG SPECT significant hoger te zijn (77% versus 57%). Na logistische regressie analyse van de FDG en ^{201}Tl rust-redistributie gegevens bleek mismatch tussen perfusie en metabolisme de hoogste voorspellende waarde te hebben voor herstel van funktie. Daarom lijkt FDG SPECT van grotere waarde te zijn dan rust-redistributie ^{201}Tl SPECT voor het herkennen van patienten bij wie de regionale en globale LV funktie zal verbeteren na een revascularisatie procedure.

Een vergelijkende studie tussen FDG SPECT en LDDE wordt beschreven in hoofdstuk 9. Het voorspellen van een verbetering van de LV funktie na revascularisatie procedure blijkt met beide technieken goed mogelijk te zijn. Echter, in segmenten met een licht verminderde wandbeweging overschatten beide technieken, maar met name LDDE, het postoperatieve herstel (specificiteit 45% versus 74% voor SPECT). Dit vormt geen belangrijke beperking, gezien het feit

dat de diagnostiek van myocardiale vitaliteit met name van belang is bij patienten met ernstige wandbewegingsstoornissen.

In hoofdstuk 10 wordt het verloop van herstel van de LV funktie na CABG beschreven. De patienten werden tot 1 jaar na de operatie vervolgd. De toegevoegde waarde van de combinatie van een hoge met een lage dosis dobutamine tijdens stress echocardiografie werd tevens onderzocht. De globale LV funktie was na 3 maanden in 12 van de 61 patienten verbeterd; na 1 jaar bleken zelfs 19 patienten herstel te vertonen. Een bifasische reaktie op dobutamine stimulatie, gedefinieerd als een verbetering van de wandbeweging tijdens een lage dosis met vervolgens een verslechtering tijdens hogere dosering, bleek een goede indicator te zijn voor het voorspellen van regionaal funktie herstel. Na 3 maanden bleek 63% en na 1 jaar zelfs 75% van de segmenten met een bifasisch patroon te verbeteren. Alle andere patronen na dobutamine stimulatie waren in hoge mate voorspellend voor het ontbreken van herstel. Dysfunktionerend myocard, met zowel aanwijzingen voor vitaliteit als voor induceerbare ischemie, bleek een grotere kans op postoperatief herstel te hebben dan vitaal myocard zonder tekenen van induceerbare ischemie. Zoals reeds in hoofdstuk 9 werd beschreven, blijkt de positief voorspellende waarde van de test afhankelijk te zijn van de ernst van de wandbewegingsstoornis. De beste diagnostische nauwkeurigheid wordt gevonden in akinetische segmenten. Na 1 jaar follow-up bleek herstel van de globale LV funktie goed te kunnen worden voorspeld met dobutamine stress echocardiografie. Een verbetering van de ejektie fraktie met meer dan 5 procentpunten werd geconstateerd in 68% van de patienten met ≥ 4 segmenten met een bifasische respons. Concluderend kan worden vastgesteld, dat het herstel van de LV funktie 3 maanden na CABG van patienten met een chronische ischemische cardiomyopathie nog niet is voltooid. De nauwkeurigheid waarmee dobutamine stress echocardiografie herstel van de LV funktie voorspelt, lijkt samen te hangen met 1) de combinatie van lage en hoge doses dobutamine stimulatie, 2) de ernst van de wandbewegingsstoornis, en 3) het tijdstip van evaluatie.

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Dankwoord

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Curriculum Vitae and List of Publications

Curriculum Vitae

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Education

1972 - 1978	Rijks Scholen Gemeenschap, Harlingen Atheneum B
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Postgraduate training

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Professional Societies

Since 1994 Member of the working group on "Nucleaire cardiologie en cardiovasculaire MRI" of the Dutch Society of Cardiology.

Since 1996 Member of the working group on Coronary Circulation of the European Society of Cardiology.

List of Publications

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